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^{CE} Perspectives on POC diabetes testing

Reducing the need for invasive lung biopsies
Preanalytical errors and critical variables in POCT
Urine drug testing: Is your your lab legally exposed?

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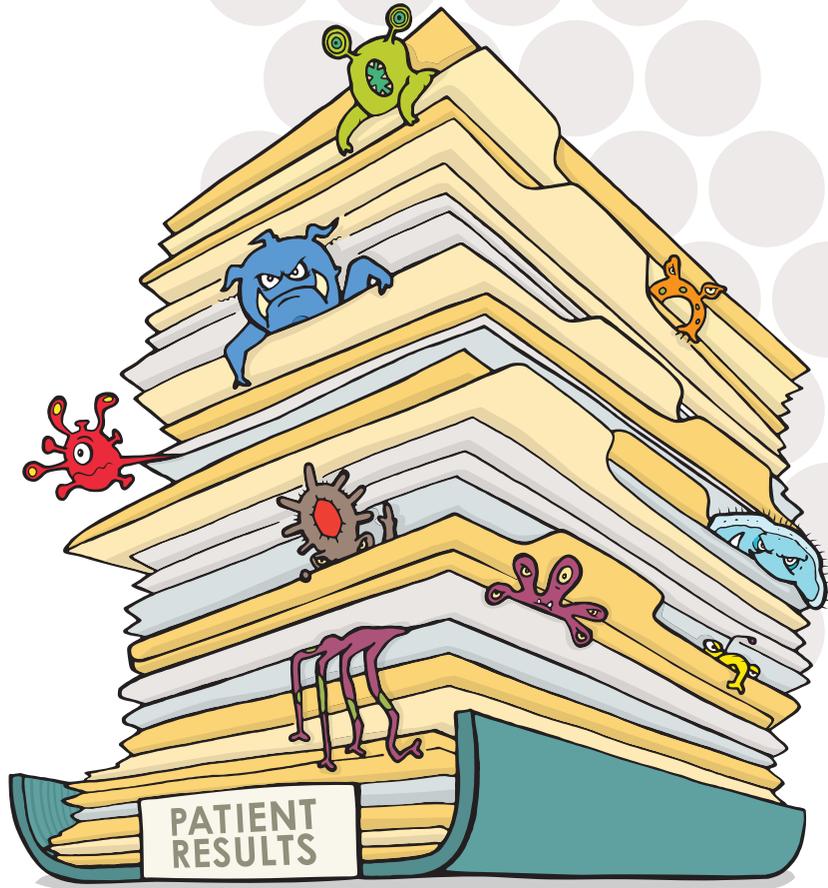
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MEDICAL LABORATORY OBSERVER



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Turn on, tune in, be careful



I was born in 1953, which means I just turned 65. It also means that I bore witness to events in American life that are the stuff of history books to some readers. (Yes, at age 10, I watched the Ed Sullivan show the night the Beatles made their first appearance. Do you know what the Ed Sullivan show was? I hope you've heard of the Beatles....)

It also means I lived through the tumultuous time in the national narrative known as "the Sixties," a time that has come to be associated with enormous cultural and social change. Two things about the Sixties: first, they really lasted from about 1966 through 1974, if you are referring to the period of cultural upheaval; the first half of the '60s was more like the '50s. Second, the country changed less, and less uniformly, than some cultural historians will have us believe. There were new ways of acting and thinking, but not for everyone, and not everywhere, and not necessarily for good (in both senses). Social change usually happens gradually, and I for one am enough of a conservative to think that is mostly a good thing.

One thing did truly change, though: middle-class American teens began to use marijuana and hallucinogens in much greater numbers than ever before. LSD guru Dr. Timothy Leary told a generation to "turn on, tune in, drop out," and it listened to him. In the high-rise dorm where I lived when I was a college freshman, many kids used marijuana (and more) almost every night. It was part of their daily social life. Ten years earlier in the same place, that had not been the case.

What makes me think about that? The occasion for my mental meanderings is a story I read in the *Wall Street Journal* (WSJ) the other day (May 7). The story indicates that, with the stigma against the use of marijuana and psychedelics fading, science is discovering that these drugs might have significant clinical utility.

The article, "The New Science of Psychedelics," says that scientists at Johns Hopkins, UCLA, and other institutions are finding that psychedelic drugs, when administered in an appropriately controlled therapeutic setting, can be potent tools to treat mental illness. Psilocybin, a chemical cousin to LSD, has shown promise as a treatment for depression. It has also helped people who are addicted to alcohol and tobacco break the habit. In December 2016, the *Journal of Psychopharmacology* published two studies of phase 2 trials in which psilocybin was given to cancer patients suffering from depression and anxiety. In the studies, up to 80 percent of the subjects showed clinically significant improvements that lasted six months or more.

The WSJ story reveals that studies of the clinical efficacy of psychedelic substances, which are not physically addictive, are not new; some were conducted in the 1950s, and in some parts of Canada psychedelic therapy was an accepted treatment for alcoholism. What put a stop to such research was the bad reputation that developed around such drugs during "the Sixties." It makes sense that, now that the medical use of marijuana is becoming increasingly accepted, and more and more people and places are at least entertaining the idea of the legalization of recreational marijuana, psychedelics are reemerging as a feasible subject for study.

The most important phrase in the WSJ article, however, is "when administered in a supportive therapeutic setting." It is worrisome to think of individuals trying to self-medicate in this way. Those dorm rooms of my college days were not exactly therapeutic settings. Even more than most research, studies of the therapeutic effects of psychedelics must clear both scientific and ethical hurdles if they are to proceed.

What the direct implications of this for the clinical lab will be remains to be seen. It would seem, though, that new kinds of therapeutic drug monitoring will become part of your work. And, knowledge of patients' prescription histories will be especially important in reporting results of drugs-of-abuse testing. That is an issue that could have legal ramifications. (See the "Clinical Issues" article on page 32.)

Alan Lenhoff



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The E.R. in the U.S.

Here are some interesting numbers related to Emergency Departments in the United States, from the Centers for Disease Control and Prevention (CDC).

141.4 million

Is the number of annual Emergency Department visits.

40 million

Is the number of injury-related visits.

45.1

Is the number of visits per 100 persons.

11.2 million

Is the number of visits that result in hospital admission.

1.8 million

Is the number of Emergency Department visits resulting in admission to a critical care unit.

32.2 percent

Is the proportion of patients seen in less than 15 minutes.

7.9 percent

Is the proportion of visits resulting in hospital admission.

1.9 percent

Is the proportion of visits resulting in transfer to a different (psychiatric or other) hospital.

• Source: <https://www.cdc.gov/nchs/fastats/emergency-department.htm>

Molecular Diagnostics

Cancer “signature” is a first step toward a blood test for lung cancer patients. A discovery by Australia-based researchers could help to identify patients with a particularly aggressive type of lung cancer who are likely to respond to immunotherapies currently used to treat other cancers. Their research also revealed a unique molecular signature in the blood that could, in the future, be used to detect these aggressive lung cancers with a simple blood test.

Walter and Eliza Hall Institute cancer researchers Dr. Sarah Best and Dr. Kate Sutherland led the research, working with colleagues at Metabonomics Australia at the Bio21 Institute, University of Melbourne. The study was published in *Cell Metabolism*.

The study focused on the role of two cell signaling pathways—KEAP1/NRF2 and PI3K—which are known to be involved in adenocarcinomas.

“More than one in five lung adenocarcinomas have alterations in the KEAP1/NRF2 pathway, suggesting it is a major cancer driver,” Sutherland says. “These cancers are very aggressive, are resistant to standard therapies, and have a poor prognosis, so new therapies are urgently needed.”

Best says that the study revealed that the tumors had characteristics indicating they were likely to respond well to immunotherapy: “Using pre-clinical models, we showed for the first time that these tumors have the ‘markers’ that respond to anti-PD-1 and anti-CTLA-4 immunotherapies, which are some of the most exciting new cancer therapies being investigated in the clinic.

“But more importantly, we showed that these immunotherapies were effective in fighting the tumors and leading to tumor regression in our preclinical models.”

Best says the research showed that non-stop signaling caused by mutations in the KEAP1/NRF2 and PI3K pathways caused lung adenocarcinomas to develop. “This is the first time anyone has shown that these alterations directly cause lung adenocarcinomas. With this knowledge, we can further investigate how targeting those pathways could lead to therapies for these aggressive and hard-to-treat cancers,” she adds.

Sutherland says the unique molecular signatures found in the blood could be a tool to identify patients who would respond to

immunotherapies, or even as the basis of an early detection test for those cancers.

Oncology

Blood cancer precursor is found in 9/11 firefighters. A study published in *JAMA Oncology* reports that New York City firefighters exposed to the 9/11 World Trade Center disaster site face an increased risk for developing MGUS (monoclonal gammopathy of undetermined significance), which can lead to the blood cancer multiple myeloma. The study was conducted by researchers at Albert Einstein College of Medicine, Montefiore Health System, the Fire Department of the City of New York (FDNY), and Memorial Sloan Kettering Cancer Center.

In MGUS, the blood’s plasma cells produce an abnormal protein called monoclonal protein that can be detected with blood tests. MGUS generally causes no problems but can progress to multiple myeloma, a blood cancer diagnosed in about 30,000 Americans each year. In multiple myeloma, rapidly proliferating plasma cells can crowd out the bone marrow’s normal blood-forming cells, leading to problems including anemia (shortage of red cells) and leukopenia (shortage of white cells). Most multiple myeloma cases are diagnosed in people older than 65.

Previous studies suggest that MGUS and multiple myeloma tend to develop after exposure to toxic chemicals. The aerosolized dust from the collapsed towers exposed FDNY and other first responders to unprecedented levels of polychlorinated biphenyls, polycyclic aromatic hydrocarbons, dioxins, asbestos, and other potential carcinogens, as well as diesel smoke from heavy machinery used in the 10-month rescue-and-recovery effort.

The study population was limited to 781 white, male WTC-exposed firefighters aged 50 to 79 whose blood samples were evaluated to assess the prevalence of MGUS in the group. When results were compared with MGUS prevalence in a non-exposed comparison group, the prevalence of MGUS in the firefighters was nearly twice as high (7.63 cases of MGUS per 100 firefighters vs. 4.34 cases per 100 non-exposed persons).

In a separate analysis, the researchers examined the 16 cases of multiple myeloma diagnosed between

September 12, 2001, and July 1, 2017, among all white, male WTC-exposed FDNY firefighters. Their average age of diagnosis was 57, or 12 years younger than the average age for multiple myeloma diagnosis nationally.

Chemistry

Stanford scientists find possible autism biomarker in cerebrospinal fluid.

Autism diagnosis is slow and cumbersome, but new findings linking the hormone vasopressin to social behavior in monkeys and autism in people may change that. Low vasopressin in cerebrospinal fluid was related to less sociability in both species, indicating the hormone may be a biomarker for autism. A paper describing the research, which was led by scientists at the Stanford University School of Medicine and the University of California-Davis, will be published in *Science Translational Medicine*.

Autism, a developmental disorder characterized by impaired social abilities, affects 1 in 68 U.S. children. Research has shown that early, intensive behavioral treatment is beneficial. Yet many children don't receive a timely diagnosis. A biological test, with a specific lab measurement indicating autism, could make diagnosis faster.

The current researchers looked for autism biomarkers in rhesus monkeys, a species whose social capabilities are reasonably comparable to those of humans. From 222 male animals, the scientists selected 15 with naturally low sociability and compared them with 15 monkeys with naturally high sociability on several biological parameters.

The scientists measured levels of two hormones, oxytocin and vasopressin, in the monkeys' blood and in their cerebrospinal fluid, which bathes the brain. Both hormones are peptides implicated in a variety of social roles, including parental care and bonds between mates. Some prior studies have hinted that these hormones may also be involved in autism.

Monkeys in the less social group had significantly less vasopressin in their cerebrospinal fluid than monkeys in the more social group. These vasopressin levels accurately predicted the frequency with which individual monkeys participated in social grooming, an important social activity for rhesus monkeys. Vasopressin blood levels were not different

between the two groups. In a group of 10 monkeys, whose cerebrospinal fluid was sampled four times over four months, the scientists showed that vasopressin levels in the fluid were stable over time.

The researchers also compared vasopressin levels in cerebrospinal fluid of 14 boys with autism and seven age-matched children without autism. Children with autism had lower vasopressin levels than children without autism, the study found.

Hematology

Blood type O patients may have higher risk of death from severe trauma.

Blood type O is associated with high death rates in severe trauma patients, according to a study published in the open access journal *Critical Care*. The study involved 901 Japanese emergency care patients with severe trauma who were transported to either of two tertiary emergency critical care medical centers in Japan during 2013 to 2016.

Researchers at Tokyo Medical and Dental University Hospital found that severe trauma patients (those with an injury that has the potential to cause long-term disability or death) with blood type O had a death rate of 28 percent, compared to 11 percent in patients with other blood types.

Dr. Wataru Takayama, the corresponding author, says: "Recent studies suggest that blood type O could be a potential risk factor for hemorrhage. Loss of blood is the leading cause of death in patients with severe trauma, but studies on the association between different blood types and the risk of trauma death have been scarce. We wanted to test the hypothesis that trauma survival is affected by differences in blood types."

Patients with blood type O have been shown to have lower levels of von Willebrand factor (vWF), a blood clotting agent, than those with other blood types. Lower levels of vWF may be linked to higher levels of hemorrhage. The authors suggest that a lower level of vWF may explain the higher death rate in trauma patients with blood type O. Takayama says that the results also raise questions about how emergency transfusion of O type red blood cells to a severe trauma patient could affect homeostasis and whether type O is different from other blood types in that regard.

The authors caution that all the patients whose data was analyzed in

this study were Japanese and that therefore there is a need for further research to understand whether the findings apply to other ethnic groups. Additionally, there was no evaluation of the impact of the individual blood types A, AB, or B, on severe trauma death rates. Instead, the authors compared type O to non-O blood type, which may have diluted the effect of individual blood types on patient survival.

Infectious Diseases

New Lyme disease tests could offer quicker, more accurate detection. New tests to detect early Lyme disease—which has been increasing beyond the summer months—could replace existing tests that often do not clearly identify the infection before health problems occur.

In an analysis published in *Clinical Infectious Diseases*, scientists from Rutgers University, Harvard University, Yale University, the National Institute of Allergy and Infectious Diseases of the National Institutes of Health, and other academic centers, industry, and public health agencies say that new diagnostic methods offer a better chance for more accurate detection of infection from the Lyme bacteria.

Lyme disease is the most common tick-borne infection in North America and Europe. There are currently more than 300,000 cases of Lyme disease annually in the United States alone, and the disease is increasing and spreading into new regions. Lyme disease frequently, but not always, presents with a bull's-eye rash. When the rash is absent, a laboratory test is needed.

The only FDA-approved Lyme disease tests, based on technology developed more than two decades ago, rely on detecting antibodies that the body's immune system makes in response to the disease. These antibody-based tests are the most commonly used tests for Lyme disease and are the current standard.

One problem, however, is that many people produce similar—called "cross-reactive"—antibodies in response to other bacteria not associated with Lyme disease. This can reduce assay specificity. Researchers say more specific testing would help doctors decide when to prescribe the antibiotics used to clear the infection and help patients avoid severe, long-term health problems. 📌

Clinical, operational, and financial perspectives of POC diabetes testing

By Connie Mardis, MEd

Diabetes is a complex, chronic illness that requires continuous medical care beyond glycemic control. Ongoing patient education and support are critical to preventing costly acute complications and reducing the risk of long-term complications that can significantly decrease quality of life.

Point-of-care testing (POCT) is one tool that can improve opportunities to educate patients and positively impact outcomes. This article examines advances in POC HbA1c standardization, and key performance indicators, including practice efficiency, outcomes, and patient satisfaction. Finally, perceived barriers to implementing a POCT program are discussed, and in that context quality control, operational, and financial concerns are addressed.

The 2018 American Diabetes Association (ADA) Standards of Medical Care in Diabetes state that the use of point-of-care HbA1c testing may provide an opportunity for more timely treatment changes during encounters between patients and providers.¹ To appreciate the clinical value of diabetic testing at the point-of-care, it is critical to understand the increasing burden diabetes is placing on patients and healthcare costs, as well as the positive impact of maintaining glycemic control.

The high cost of diabetes

Diabetes is a treatable disease and yet is among the major causes of death in most developed countries. It is one of the largest health emergencies of the 21st century, and one of four priority non-communicable diseases targeted for action by world leaders.²

The global prevalence of diabetes has nearly doubled since 1980, rising from 4.7 percent to 8.5 percent, and it is steadily increasing.² The 2017 National Diabetes Statistics Report estimated that in the United States 30.3 million people, or 9.4 percent of the U.S. population, have diabetes. This number includes the estimated 7.2 million people who are undiagnosed. The percentage of adults with

diabetes increases with age, reaching a high of 25.2 percent among those aged 65 years or older.³

Risk factors for complications of diagnosed diabetes include smoking, obesity, physical inactivity, high blood pressure, high cholesterol, and high blood glucose.⁴ With clear links to multiple comorbidities such as cardiovascular disease, kidney disease, infections, malignancy, and functional impairment, diabetes places a tremendous financial burden on both patients and healthcare systems.

Total medical costs and lost work and wages for people with diagnosed diabetes in the U.S. is \$245 billion. Average medical expenditures among diagnosed diabetics were about 2.3 times higher than expenditures for people without diabetes.³

Self-monitored blood glucose testing

Integrating self-monitored blood glucose (SMBG) results into diabetes management can be a useful tool for guiding medical nutrition therapy and physical activity. Indeed, major clinical trials of insulin-treated patients have included SMBG as part of multifactorial interventions and demonstrate the benefit of intensive glycemic control on diabetes complications.¹ Thus, SMBG remains an integral component of effective therapy for type 1 and some type 2 patients. However, the evidence is insufficient regarding when to prescribe SMBG and how often testing is needed for patients with type 2 diabetes using oral agents.¹

Of concern is that many patients who check their blood glucose at least once daily report taking no action when results are high or low. Patients should be taught how to use SMBG data to adjust food intake, exercise, or pharmacologic therapy within prescribed limits to achieve specific glycemic goals.

Glucose testing vs. HbA1c

In the laboratory, measurement of glucose in the plasma of fasting subjects is widely accepted. There are significant advantages to glucose testing, including the existence of inexpensive assays on automated instruments that are available in most laboratories worldwide. However, measurement of glucose in the blood is subject to several limitations, some of which are not widely appreciated.⁵

Samples for fasting glucose analysis should be drawn after an overnight fast of at least eight hours with no caloric intake. But glucose measurement can be affected by several preanalytical variations:

- The concentration of glucose in the blood can be altered if the patient has not adhered strictly to the eight-hour fast or has fasted for a more prolonged period, and it also can be affected by exercise. The fasting issue is a considerable practical problem, as patients are usually not fasting when they visit the doctor, and it is often inconvenient to return for phlebotomy.
- Glucose concentrations decrease in the test tube by five percent to seven percent per hour due to glycolysis, the

continued on page 10

Earning CEUs

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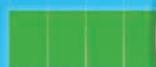
Upon completion of this article, the reader will be able to:

1. Discuss the economic and healthcare burden of diabetes in the United States.
2. List advantages and disadvantages of glucose testing versus HbA1c testing.
3. Discuss the benefits of strict management and control of diabetes through long-term testing.
4. Explain the progression and outcomes of POCT testing in the physician office setting and in other healthcare settings.

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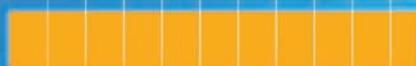
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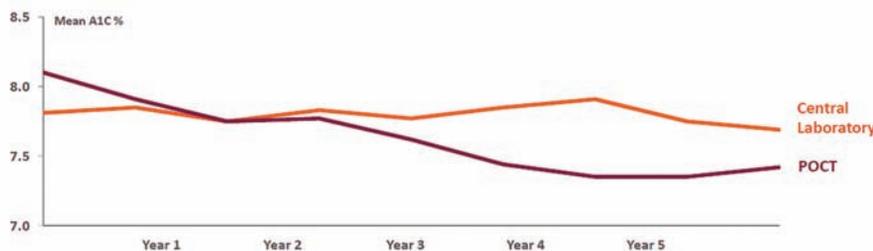


Figure 1. HbA1c results at the point-of-care vs. the central laboratory.

breakdown of glucose by enzymes, which releases energy and pyruvic acid.⁵

- Glucose concentrations can be altered by acute stress. If a patient has trouble finding parking or is frustrated by a long wait at the medical facility, that could affect the numbers.⁵

In contrast, fasting is not required for HbA1c testing. HbA1c is formed by the nonenzymatic attachment of glucose to hemoglobin. Since the life span of red blood cells is approximately 120 days, HbA1c represents the average glucose concentration over the preceding eight to 12 weeks.⁵

Landmark studies such as the Diabetes Control and Complications Trial (DCCT) (type 1 diabetes) and the United Kingdom Prospective Diabetes Study (UKPDS) (type 2 diabetes) emphasize the role for HbA1c in diabetes management.¹ A link between HbA1c and diabetic complications was confirmed and the need for adequate glycemic control underscored.¹

Furthermore, the Kumamoto Study and the UK Prospective Diabetes Study (UKPDS) confirmed that intensive glycemic control significantly decreased rates of microvascular complications in patients with type 2 diabetes. Long-term follow-up of the UKPDS patients showed enduring effects of early glycemic control on most microvascular complications. After 10 years of observational follow-up, patients originally randomized to intensive glycemic control had significant long-term reductions of 13 percent in myocardial infarction and 27 percent reduction in all-cause mortality. Achieving HbA1c targets of < seven percent or 53 mmol/mol has been shown to reduce microvascular complications of diabetes.¹

The ADA Standards address frequency of HbA1c testing, noting that it should be performed routinely in all patients with diabetes at initial assessment and as part of continuing care.¹ Measurement approximately every three months determines whether patients' glycemic targets have been reached and maintained. Patients with type 2 diabetes with stable glycemia well within target may do well with HbA1c testing only twice per year. Unstable or intensively managed patients, for example pregnant women with type 1 diabetes, may require testing more frequently than every three months.¹

ACR and early warning of kidney disease

In addition to regular HbA1c monitoring, yearly urine albumin-to-creatinine ratio (ACR) tests are recommended for patients with diabetes to identify progression of kidney failure.⁶

Far more convenient to the patient and healthcare provider than a 24-hour urine collection, an ACR measurement is reported in mg albumin/g creatinine and is widely accepted as an indicator of kidney function. Currently, the National Kidney Foundation defines an ACR range from 30 to 300

mg/g as above normal, and multiple tests in this range over a three-month period suggest a problem.⁷

The impact of chronic kidney disease (CKD) extends beyond just a diminished quality of life for those affected by the disease; it also represents more than \$1 trillion in healthcare costs over the next decade.⁸ But if CKD is

detected early and managed appropriately, the deterioration in kidney function can be slowed and the risk of associated cardiovascular complications reduced.⁹

Laboratory quality at the point of care

The ability of a POC instrument to most closely replicate the actual HbA1c of any given patient is essential. As new HbA1c POC devices have been introduced to the market, standardization has become increasingly important to ensure integrity and equivalence to conventional lab procedures. Devices should meet quality measures set by the National Glycohemoglobin Standardization Program (NGSP) for clinical results to be considered reliable and accurate.¹⁰

Since its development in 1996 under the direction of the American Association for Clinical Chemistry, the NGSP has been the authority in establishing guidelines and protocols for standardizing HbA1c testing for both POC and laboratory instruments to Diabetes Control and Complications Trial (DCCT)-equivalent values. This tight criterion provides practitioners confidence in the accuracy and precision of these devices. Based on the stringent criterion set by the NGSP and its alignment with DCCT results, the ADA endorsed the NGSP and specifically recommends that labs use only methods that have passed NGSP certification.¹⁰

Currently, a few of the POC devices on the market have met NSGP criteria for analytical performance, making them acceptable options for POC HbA1c testing.¹⁰

Studies support POC HbA1c testing

Clinically, a number of studies have found that POCT was associated with a significant reduction in HbA1c over 12 months. An even more sustainable benefit of POC HbA1c results was demonstrated in a large, retrospective, cross-sectional study. Significant HbA1c improvements associated with POC testing were detectable in the short and long term (Figure 1).¹¹

In addition, POCT including HbA1c testing has been shown to significantly improve clinical operations with cost reductions through improved practice efficiency. Following implementation of POCT, one study reported a 21 percent decrease in tests ordered per patient ($P < .0001$); a decrease in follow-up phone calls and letters by 89 percent and 85 percent, respectively ($P < .0001$ and $P < .0001$); and a 61 percent decrease in patient revisits ($P = .0002$).¹² Estimated testing revenues exceeded expenses by \$6.62 per patient, and potential cost savings from improved efficiency were \$24.64 per patient. The authors noted that the economic benefits of POCT may be realized in both fee-for-service and global payment environments.¹²

After implementing POCT for HbA1c, lipid panel, and comprehensive metabolic panel in a primary care practice, another study monitored patient satisfaction using an anonymous survey. On a scale of 1 (poor) to 4 (excellent), the score was 3.96; both the patient

continued on page 12

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continued from page 10

comments and results strongly indicated a high level of patient satisfaction with onsite POCT.¹³

Overcoming perceived barriers

Perceived obstacles to implementing a POCT program have included accountability factors such as quality control, adequate staff training, and oversight for accreditation purposes.¹⁴

For POCT devices operating under the central laboratory license, the single biggest challenge to the adoption of POCT is maintaining control, regulatory compliance, and training records for thousands of operators performing testing on hundreds of devices in anywhere from 30 to 50 locations within the hospital system.¹⁵

In the past, the challenge of maintaining separate POCT data management systems, or middleware, for each manufacturer's products to interface with the hospital and laboratory information systems (HIS and LIS) has added complexity and increased software licensing costs.¹⁶ However, advances include an open-access data management system that can connect more than 160 POC devices, including HbA1c analyzers and glucometers, from all manufacturers (Figure 2).¹⁶

A manufacturer-independent solution helps ensure IT investment protection in the event a hospital changes POC equipment vendors at the main hospital or in any spoke hospital, clinic, or physician office across the enterprise.

An open-access data management system can automatically validate and transfer patient results obtained from POCT devices to the electronic medical record to facilitate billing capture and monitor and manage data, POCT devices, and operators. POC coordinators can proactively manage enterprise-wide external quality assessment (EQA) results according to accreditation requirements. Distributions and statistics are easily viewed and filtered with the familiar proactive traffic-light display that flags non-compliances in any connected POCT devices at any site, improving workflow.¹⁶

The content of e-learning courses and tests, supplied by each POCT device manufacturer to the open-access data management system, guarantees that only approved content is used for training. When an operator passes the test, indicating successful completion of a course, the results are automatically documented in eLearning, and a message is sent to the data management system, which automatically extends the operator's certification for another year.¹⁶

An open-access data management system is a key enabler for POCT coordinators. It connects devices from any manufacturer and provides operator oversight so testing efficiency is maximized, clinical workflow is improved, compliance is adhered to, and costs are efficiently managed.

POC HbA1c today

Regular HbA1c measurement is recommended by ADA and international guidelines for all patients with diabetes for the assessment of glycemic control by providing information on long-term glycemic status and reliably predicting risk for diabetes-related complications. Accurate, NGS-standardized POC HbA1c devices are available, and advances in open-access data management can streamline regulatory compliance as well as operator and device management enterprise-wide.

POC HbA1c devices have improved the quality of diabetes management by offering healthcare providers a method for timely assessment of diabetes control, which facilitates informed decision making during consultations. Furthermore, POC HbA1c devices may improve patient adherence and satisfaction by lessening transportation and cost barriers associated with extra office and laboratory visits. ↻

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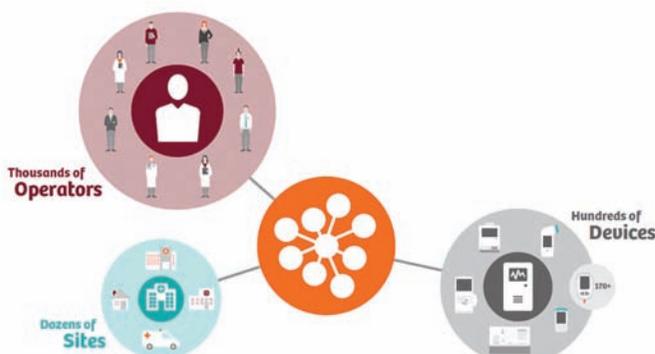


Figure 2. Open POC data management system improves workforce productivity enterprise-wide.

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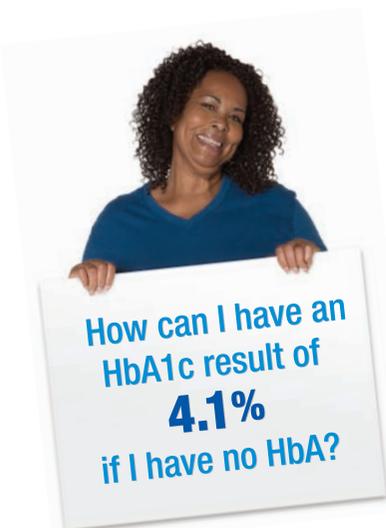
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TEST QUESTIONS Circles must be filled in, or test will not be graded. Shade circles like this: ● Not like this: ⊗

1. Since 1980, the global prevalence of diabetes has
 - a. decreased.
 - b. stayed the same.
 - c. almost doubled.
 - d. almost tripled.
2. Which are associated risk factors for those with diabetes?
 - a. smoking, physical activity, and lack of sleep
 - b. smoking, obesity, and physical inactivity
 - c. high blood pressure, high cholesterol, and high blood glucose
 - d. both b. and c
3. Comorbidities clearly associated with diabetes include all but
 - a. cardiovascular disease.
 - b. osteoarthritis.
 - c. kidney disease.
 - d. malignancy.
4. Self-monitored blood glucose (SMBG) can be a useful tool for guiding nutritional therapy and physical activity.
 - a. True
 - b. False
5. There is insufficient evidence for integrating SMBG analysis into diabetes management for patients who are
 - a. taking oral agents.
 - b. diagnosed as prediabetic.
 - c. insulin-treated.
 - d. none of the above
6. What factor(s) can alter the concentrations of a fasting glucose level?
 - a. noncompliance with an eight-hour fast
 - b. glycolysis
 - c. acute stress
 - d. all of the above
7. HbA1c levels represent the average glucose concentration over the past
 - a. 2-4 weeks.
 - b. 5-7 weeks.
 - c. 8-12 weeks.
 - d. 15-20 weeks.
8. Studies by the DCCT and UKPDS have concluded that there is not a link between HbA1c and diabetic complications.
 - a. True
 - b. False
9. Microvascular complications of diabetes has been reduced by achieving an HbA1c result of
 - a. less than one percent.
 - b. less than three percent.
 - c. less than five percent.
 - d. less than seven percent.
10. Which test is recommended annually for identification of kidney failure progression in diabetic patients?
 - a. urinalysis
 - b. urine albumin-to-creatinine ratio
 - c. estimated GFR
 - d. serum-to-urine creatinine ratio
11. What range of the ACR indicates kidney disease progression?
 - a. 10-30 mg/g
 - b. 30-300 mg/g
 - c. 30-300 mg/dl
 - d. 300-1000 mg/g
12. If CKD is detected early and managed well, the deterioration in kidney function can be slowed.
 - a. True
 - b. False
13. Which program establishes strict guidelines and protocols for standardizing HbA1c POC testing in physician offices?
 - a. UKPDS
 - b. DCCT
 - c. ADA
 - d. NGSP
14. POC testing in physician office labs is associated with improvement in which area(s)?
 - a. clinical cost-reduction
 - b. patient economic benefits
 - c. HbA1c result
 - d. all of the above
15. Implementation of which test(s) resulted in high levels of patient satisfaction with onsite POCT?
 - a. HbA1c only
 - b. HbA1c and lipid panel
 - c. HbA1c, lipid panel, and comprehensive metabolic panel
 - d. lipid panel and comprehensive metabolic panel
16. The only perceived obstacle to implementing a POC program is the oversight guidance for accreditation purposes.
 - a. True
 - b. False
17. What is/are the biggest challenge(s) to POCT devices that are operated under the central laboratory license?
 - a. maintaining control of the devices
 - b. overseeing regulatory compliance
 - c. keeping up-to-date training records on hundreds of employees
 - d. all of the above
18. What advancement has helped the management of accreditation requirements of POCT within a healthcare organization?
 - a. open-access data management system
 - b. closed-access data management system
 - c. LIS with increased software licensing programs
 - d. none of the above

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Preanalytical errors and critical variables in POCT

By Aparna Jha Ahuja, MD

Today's "smart" technology enables us to have important information at our fingertips. Point-of-care testing (POCT)—also referred to as "near patient, bedside, and extra-laboratory testing"¹—offers the rapid delivery of healthcare information as well.

Centralized laboratory testing was the standard until the mid-1980s. Since that time, many laboratory tests (e.g., glucose and blood gas testing) have transitioned to patient care settings, including physicians' offices, ambulances, and hospital units (e.g., the intensive care unit, emergency department, surgical suites), as well as clinics, dialysis centers, and nursing homes.² Devices for POCT range in size from small handheld meters for glucose monitoring to larger benchtop analyzers for hematology.

The surge in POCT may be attributed to distinct advantages over core laboratory testing, fewer sample workflow steps (Table 1), faster test turnaround time, more timely triage or treatment, potential decrease in hospital length of stay, and lower sample volume requirements.

Specimen Workflow Core Laboratory vs. Point-of-Care Testing	
Test Order Received Personnel Assigned Supplies Gathered Site Prepared Samples Collected	
Core Laboratory Testing	Point-of-Care Testing
<ul style="list-style-type: none"> • Sample Packaged for Transport to Lab • Sample Transported to Lab • Sample Received in Lab • Sample Prepared for Testing • Test Performed by Lab Personnel 	<ul style="list-style-type: none"> • Test Performed by POCT Operator
Result Obtained Result Interpreted	

Table 1. Although fewer steps are required to collect specimens for POCT, the potential for error is not eliminated.

A quick result does not always mean an accurate result, however. As in the core laboratory, the preanalytical phase of the POCT process may introduce errors that could impact test results. Errors in POCT can be particularly problematic if immediate action is taken based on incorrect results obtained. Consider the consequences for a patient who receives a higher dose of warfarin based on an inaccurate test result. Receiving an excess amount of warfarin can lead to cerebral hemorrhage or gastrointestinal bleeding. Additionally, if repeat testing is necessary as a result of the incorrect result, the time for obtaining diagnosis and initiating treatment may be prolonged, negating the benefits of POCT testing. This is detrimental for critical care patients who often undergo frequent testing to monitor their condition (e.g., blood gases, glucose, hemoglobin), reaffirming

the importance of quality specimens. Collecting quality specimens may be a challenge in POCT, since testing is performed outside the control of the laboratory, often by less-skilled, non-laboratory personnel, and in different clinical settings. Understanding some of the preanalytical factors that can impact POCT results goes a long way in ensuring that the results obtained are valid ones.

Patient preparation

Proper identification is of crucial importance. As in the core laboratory, accurate test results begin with correct patient identification. Not all POCT devices have built-in barcode scanners to facilitate bedside patient identification, which requires manual entry of the patient's information and increases the potential for transcription error.³ Operators must also be cognizant of similar patient surnames (Johnson vs. Johnston) and dates of birth (1/1/55 vs. 1/11/55). Verification of patient identification should occur at the bedside prior to testing. Additionally, at least two patient identifiers should be used as recommended by the Joint Commission and Clinical Laboratory and Standards Institute (CLSI).^{4,6}

Sample preparation

Use the appropriate anticoagulant. Heparin is the primary anticoagulant for testing blood gases, ionized calcium, and electrolytes. However, the amount of heparin may influence test results. Higher concentrations of liquid heparin may dilute the sample and alter the values of pCO₂, pO₂, and Ca⁺⁺. If liquid heparin is used, the ideal volume should be less than 10 percent, preferably five percent or less of the total sample volume.^{7,8} Alternatively, a balanced formulation of dry lithium heparin could be utilized to measure blood gases and electrolytes.⁹

In addition, tubes should be filled to the specified level by the manufacturer to prevent excess anticoagulant-to-blood ratio. Tubes that are overfilled will not have sufficient anticoagulant to prevent clotting.

Eliminate air bubbles. Air bubbles in arterial samples may cause a bias in blood gas measurements, particularly for pCO₂ and pO₂. Any air bubbles should be expelled by gently tapping the sides of the syringe.

Mix well. Inadequate mixing of the specimen may cause incomplete dissolution of the anticoagulant in the syringe and the formation of clots, which may negatively impact hematocrit and obstruct the analyzer probe. Mixing should be accomplished immediately after collection by inverting the syringe a minimum of five times and then rolling the syringe between the palms for five seconds.¹⁰ Vigorous mixing or agitation may cause the specimen to hemolyze.

Prevent hemolysis. Squeezing or milking the puncture site for capillary collection may contaminate the specimen with tissue fluid and cause hemolysis, which could interfere with test results (e.g., elevations in potassium, troponin, pCO₂). Since visible hemolysis is not apparent in whole blood specimens, any inconsistent results should be repeated to verify accuracy.¹¹

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Store properly. Operators should consult the recommendations provided by the manufacturer for proper storage conditions. Storing cartridges beyond these recommendations may affect test results. For instance, exposure of glucose test strips to air, light, and humidity may alter their performance.

It is important to note that whole blood specimens continue to metabolize after collection, warranting prompt analysis to avoid changes in blood gases and related parameters.^{11,12}

Training all users

To minimize the risk of errors, standard operating procedures should be established which detail best practices for each POC test on each instrument. These procedures should be coupled with continuous training for all users to ensure comprehension and competence.

Point-of-care testing is expected to increase exponentially, with the addition of more assays and instruments. As in the core laboratory, a quality preanalytical phase in POCT is key to a quality specimen. Understanding the preanalytical factors that may contribute to errors can help healthcare professionals maximize the potential of POCT for their patients. ↻

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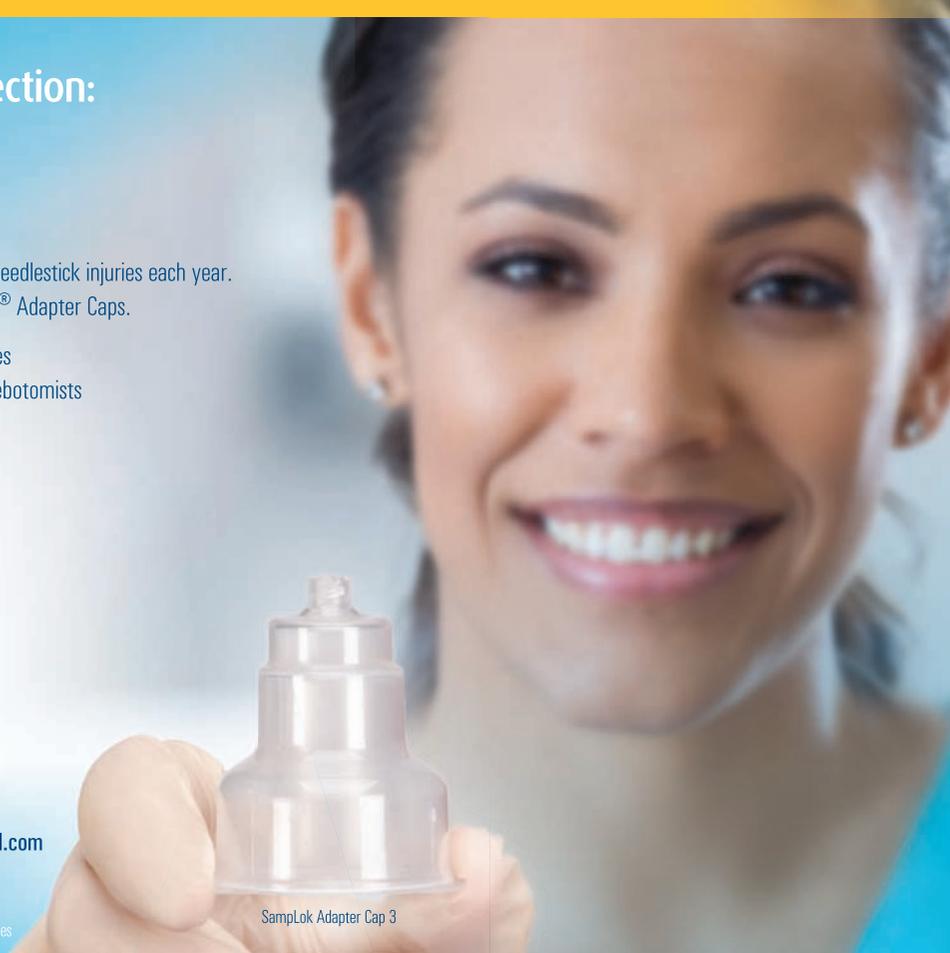
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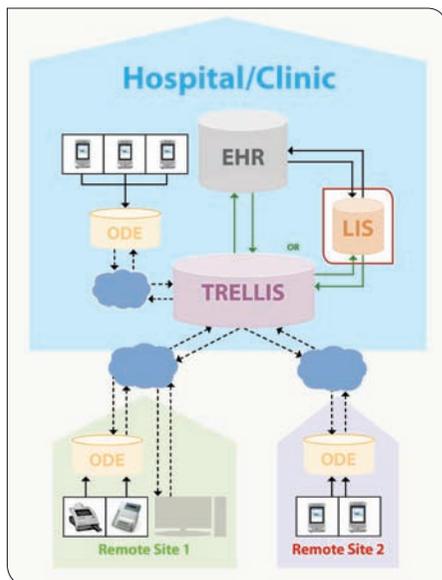
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Genomic markers for cancer

By Giulia C. Kennedy, PhD

Lung cancer diagnosis is notoriously challenging, largely because the current standard of care frequently requires invasive methods to obtain surgical tissue and, thereby, enable an accurate diagnostic call. This challenge will become more pronounced as lung cancer screening programs reach more at-risk patients across the United States. This article addresses the specific, current limitations of lung cancer diagnosis, the impact of these limitations on patients and the healthcare system, and the demonstrated ability of genomic testing to help address these limitations. It also explores the genomic discoveries and scientific advances that soon may enable even earlier detection and treatment of this disease.

Challenges of lung cancer diagnosis

Lung cancer is the leading cause of cancer-related deaths in the U.S., killing more than 150,000 Americans each year.¹ While early detection and diagnosis can significantly improve survival,²⁻⁴ presently only 16 percent of lung cancer cases are diagnosed at an early stage.⁵ In 2011, results from the U.S. National Lung Screening Trial (NLST) demonstrated that annual screening with low-dose computed tomography scan (LDCT) is an effective means to identify lung nodules and lesions earlier and thereby reduce lung cancer deaths among people at risk for the disease.⁶ As a result, in 2013 the United States Preventative Services Task Force (USPSTF) recommended annual LDCT screening for current and former smokers aged 55 to 74.⁷

Among the pulmonology community, there is significant uncertainty about the optimal work-up of pulmonary nodules and lesions, whether they are found incidentally or via LDCT screening. Current guidelines are complex and non-specific, particularly in cases where patients' nodules are not clearly benign or cancerous based on imaging and clinical workup.⁸ Bronchoscopy is the most commonly used tool to evaluate lung nodules and lesions, generally preferred over trans-thoracic needle biopsy (TTNB) and surgical lung biopsy (SLB) because it is less invasive. Unfortunately, the benefits of bronchoscopy come with some drawbacks. It is challenging to reach peripheral nodules with this tool, so when a nodule comes back with a negative result, it is not always clear whether the nodule is truly benign or was just missed. Perhaps the most problematic issue with bronchoscopy is that among the estimated 350,000 patients who undergo the procedure each year as part of a pulmonary nodule work-up, 40 to 60 percent come back non-diagnostic.⁸⁻¹⁰

Lung nodules that are not clearly benign or malignant present a significant challenge to physicians, who often pursue aggressive approaches in order to secure a definitive result and avoid missing a lung cancer diagnosis. Published

literature suggests that up to 41 percent of patients with inconclusive bronchoscopy results are referred to risky and expensive invasive procedures, including TTNB and SLB. Ultimately, up to 40 percent of these invasive procedures show that the nodule is benign, meaning patients were unnecessarily exposed to procedural risks and discomfort.¹¹ These procedures also create additional financial burden to the healthcare system: costs for SLB, for example, can exceed \$20,000.

These challenges and implications are likely to become more problematic as expanded lung-cancer screening is increasingly embraced nationwide.

The role of genomic testing

Genomic testing has demonstrated the ability to reduce ambiguity in lung cancer diagnosis and thereby reduce reliance on invasive and costly procedures such as biopsy. In 2015, a U.S.-based company introduced a 23-gene bronchial genomic classifier that complements bronchoscopy to increase its accuracy among patients undergoing a work-up for pulmonary nodules and lesions.

This classifier is based on research conducted by Dr. Avrum Spira and his team at Boston University School of Medicine, which demonstrated that cells in the central bronchial airways of the lung exhibit measurable cancer-associated gene-expression changes due to smoking. These collective genomic alterations comprise a "field of injury" which serves as a biomarker distinguishing ever-smokers with lung cancer from those with benign lung disease, independent of clinical risk factors.¹² The genomic test developers combined gene expression data and machine learning to create a classifier that effectively identifies these field-of-injury molec-

ular changes without the need to sample a lung nodule or lesion directly.

The genomic test uses cells obtained from standard cytology brushings taken from the mainstem bronchus during a lung cancer diagnostic bronchoscopy. Local pathologists review the cytology sample, and a sample is then sent to the test-maker's CLIA-certified laboratory, where genomic testing is performed if the bronchoscopy result is inconclusive.

The classifier's performance—including its ability to significantly enhance the diagnostic yield of bronchoscopy—has been verified in multiple clinical studies, including clinical validation data published in *The New England Journal of Medicine*. Findings demonstrate that the classifier improved the overall sensitivity of bronchoscopy, from 75 percent for bronchoscopy alone to 97 percent when paired with the test ($p < 0.001$). Additionally,

“Genomic testing has demonstrated the ability to reduce ambiguity in lung cancer diagnosis and thereby reduce reliance on invasive and costly procedures such as biopsy.”

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the genomic test has a high degree of accuracy (negative predictive value of 91 percent) in identifying patients who are at low (<10 percent) risk of cancer.¹³ Patients who are classified as low risk by the test can be monitored with CT imaging rather than directed to surgery.

The real-world implications of this genomic classifier have been confirmed through a prospective clinical utility study. Hogarth et al found that when the test classified patients as low risk for lung cancer, there was greater than 50 percent relative reduction in physician recommendations for invasive diagnostic procedures such as biopsy, as compared to recommendations made without genomic testing.¹⁴ In a second study, Ferguson et al concluded that a low-risk classifier result prompted a three-fold reduction (from 57 percent to 18 percent) in invasive procedure recommendations among pulmonologists, compared to when no genomic test results were available.¹⁵

In the current healthcare environment, the cost-effectiveness of any new technology must also be considered. Data published in 2017 suggest that use of the bronchial genomic classifier reduces invasive lung-cancer diagnostic procedures by 28 percent at one month and 18.3 percent at two years, and is cost-effective compared to the use of bronchoscopy alone.¹⁶

Future technologies

The science and discoveries that enabled the existing bronchial genomic classifier have created opportunities for even earlier lung cancer detection and treatment. In one very exciting recent development, researchers from Boston University demonstrated that the same field-of-injury genomic changes found in the main airway of current and former smokers with lung cancer can be detected in the nasal passages. Their findings, published in the *Journal of the National Cancer Institute*, provide evidence that molecular biomarkers used to determine lung cancer risk in cells from the bronchial airway could provide similar information as cells obtained from a simple nasal swab.¹⁷ Research is already underway to explore how this discovery could be translated into genomic tests that could enable earlier lung-cancer detection and treatment and ultimately help to reduce the number of associated deaths. 📌

Please visit mlo-online.com for references.



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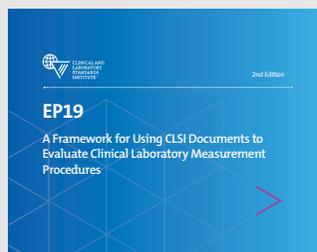
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When does it make sense to build your own test?

By Sherry Dunbar, PhD, MBA

Determining whether to address a clinical lab need through an in vitro diagnostic (IVD), a send-out reference lab test, or a laboratory-developed test (LDT) is an ongoing challenge.

Some of the complexity around this decision was recently mitigated by the U.S. Food and Drug Administration's (FDA) decision to delay guidelines that may have altered the regulation of LDTs, easing months-long uncertainty about whether these tests would continue to fall under the purview of CLIA or be subject to the same FDA approval standards as IVDs.

Even without that uncertainty, though, clinical lab leaders must regularly weigh several factors when deciding whether to develop and launch a new LDT or to find a suitable alternative. While cost is the most obvious guide for that decision, a number of other elements are equally important for leaders of a well-run lab to consider.

Clinical need

Many new LDTs trace their roots to a spate of requests for a diagnostic missing from the lab's test menu. When this demand emerges, lab leaders must review their options. First, they need to figure out whether an IVD exists to meet this need. If it doesn't, the next step is to search for a send-out test, most likely at a reference laboratory. The volume of demand is a major factor in choosing to develop a new in-house test. If the test is only needed seasonally or at low volumes, lab leaders may find that they wouldn't be able to use up a set of reagents before they expire—a strong argument against adding the test to a lab's portfolio. But if there are no good alternatives and demand is strong and sustained, then an LDT becomes a much more attractive option.

Cost considerations

From an outsider's perspective, the calculation around cost is simple: how much will it take to get a new test up and running? But clinical lab leaders know that the equation is far more complicated. Sending a test out to a reference lab or running an IVD may seem very expensive—enough to merit consideration of developing an in-house test—but it costs quite a lot to get a new LDT designed and fully validated. Assuming that per-test costs for an LDT are lower than the existing alternatives, labs must determine how many tests they would have to run to recover the substantial set-up costs. This break-even point offers useful information and helps lab directors decide whether an LDT makes sense based on cost and demand for the test.

Turnaround time

Information about which tests are available at which facility is useless without the clinical context of how quickly that data is needed to make a difference for a medical team treating a patient. For example, in a case where there is no IVD, but a send-out test is available through a reputable reference lab, an LDT still makes more sense if the send-out

test would take several days but the clinical information is needed much sooner to have a positive impact. LDTs built on molecular diagnostic platforms may make more sense for situations in which rapid results are essential. On the other hand, results that are not time-sensitive may tilt the scales toward choosing a reference lab's test.

Performance factors

Another major clinical issue is the performance of existing test options. For instance, an available IVD for the indication needed might seem quite appealing, but that changes dramatically if the sensitivity and specificity of the test are inadequate. Experienced lab directors might have a good sense of the performance they are likely to get from an LDT, and if those numbers are better than the existing IVD, that's a strong argument for developing a new test. This issue was highlighted earlier this year during flu season; the rapid influenza test used at many hospitals and clinics had a sensitivity as low as 50 percent, leading to an extremely high number of false negatives for a particularly dangerous flu strain.¹ Had a rapid LDT alternative with higher sensitivity been available, physicians with access to that lab would have been able to provide better treatment for their patients.

Staff expertise

The breadth of tests offered by a clinical lab directly reflects the range of skills available through the lab's team members. While many lab reports look the same, the skills needed to perform each test vary significantly—as do the skills needed to develop and validate a new test. The ability to launch a new LDT depends on whether the expertise is available internally to design the test. For example, many labs no longer have a parasitologist on staff. Therefore, routine parasitology tests are often sent out to reference labs, which increases the time to obtain a result. If a lab has the ability to develop LDTs, parasitology targets might be an important area to consider. In another example, molecular tests often rely on PCR primers and/or probes, and without in-house expertise, it is virtually impossible for a lab to develop molecular LDTs. There is also the matter of the lab's overall capabilities—without high-complexity certification, labs are simply unable to meet the requirements needed to develop their own tests.

Design complexity

A final element that lab members must consider is the technical complexity associated with developing a new test. In some cases, another lab will have not only designed an LDT for the specific type of assay needed, but will also have published its design and protocols, including everything from the technology platform used to primer design details. When this kind of information is readily available, the barriers to developing and validating a similar LDT drop substantially for other labs. But if there is no such information, or if published protocols require technology that's not

available to the lab looking to launch a test, the design phase is much more intensive. Labs seeking the flexibility to develop their own tests without having to continually acquire new instruments can adopt platforms that use standardized techniques, such as universal thermal cycling profiles, to reduce LDT design complexity.

Making an informed decision

Continually improving and expanding the test menu is critical to growth and sustainability for most clinical labs. Each test added represents in-depth consideration of the available options and careful calculations of the economic and clinical merits of designing new LDTs vs. other testing options. When all of the factors above are included in those calculations, lab leaders are best able to serve their healthcare communities while also giving appropriate attention to the bottom line. 🔄

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Sherry Dunbar, PhD, MBA, serves as senior director of global scientific affairs for Luminex.

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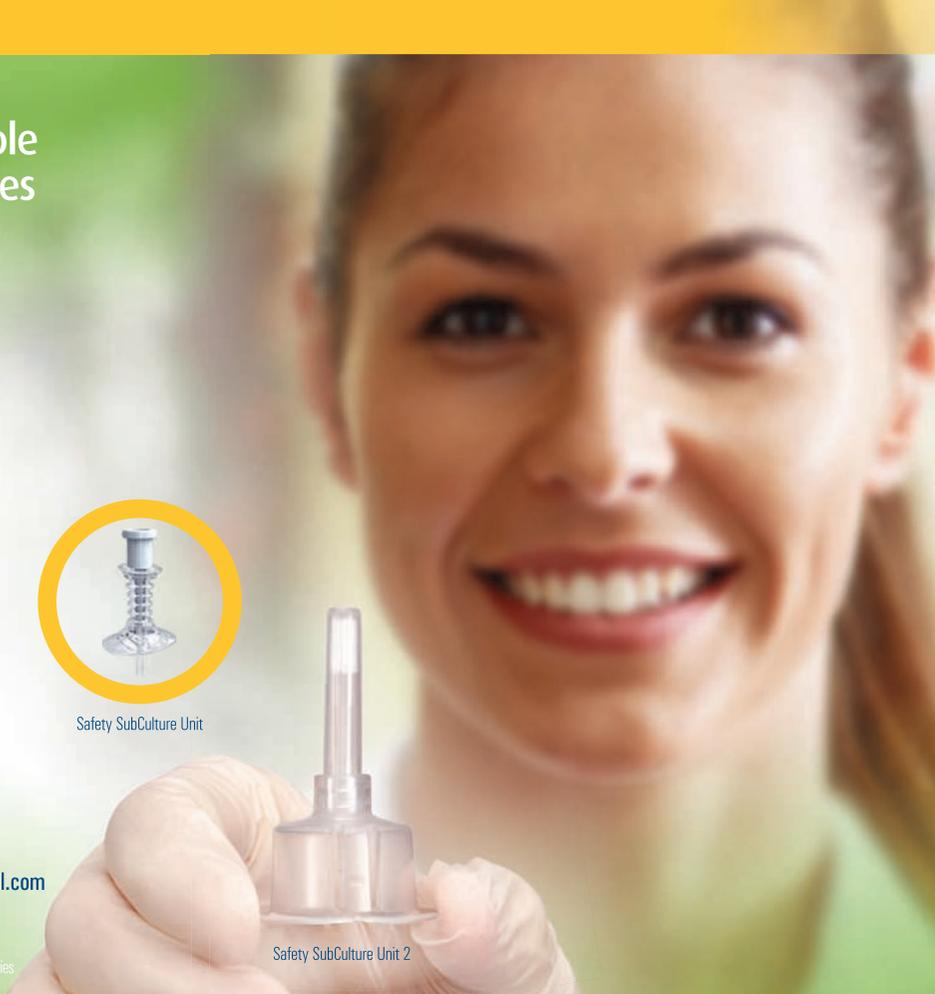
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Safety SubCulture Unit 2

Noise pollution and the lab environment

By Anthony Kurec, MS, H(ASCP)DLM

Unwanted noise has been a fact of human life for eons. With the advent of the Industrial Revolution and the subsequent development of modern technology, noise-related health issues arose, but it is a problem that has only been sporadically addressed.¹ High workplace-related noise levels are part of the challenge posed by what can only be termed “noise pollution.” Today’s clinical lab is not immune.

Moreover, a number of studies have been undertaken to address noise pollution and how it can alter laboratory findings. From these studies it is clear that chronic exposure to noise results in various levels of hearing loss and, over time, can lead to stress and related ill-health issues that may be reflected in abnormal laboratory test results. This is especially true in the very young, the aged, and the chronically ill.²

To be clear, I am talking about separate two topics related to noise and the clinical laboratory: the effects of excessive noise on human health, which can be reflected in abnormal serology values; and the stressing effect of excessive noise for laboratorians in the workplace.

Impact of noise on general health

Loud noises experienced over an extended period of time can cause hearing loss. Noises over 120 decibels (dB), experienced for even a short period of time, can have an immediate impact, causing permanent hearing damage.³ Because many offending noise sources are very common, they often go unnoticed, blending into the drone of everyday activities.

The most common issue due to noise disturbances is the interruption of sleep both in terms of quality and quantity. Studies have shown that residing near excessive noise sources can increase blood pressure, heart rates/pulses, hypertension, nausea, headaches, mood changes, and anxiousness. Poor cognitive functions, such as speech, reading, attention span, memory, and school performance, have also been seen in children residing in such environments.^{1,4,7}

Further, hearing loss is the most common occupational disability. It affects approximately 22 million people and costs up to \$242 million in healthcare disability compensation annually.⁸ Even when the National Institute for Occupational Safety and Health (NIOSH) limits are imposed, eight percent of workers could still have some hearing loss.⁵ The WHO has determined how the following decibel ranges can affect health.⁹

- <30 dB: No biological effects.
- 30–40 dB: Modest effects, mostly sleep disturbances. Most vulnerable are children and the elderly.
- 40–55 dB: Often see adverse health effects resulting in major life adjustments.
- >55 dB: Considered a dangerous public health situation with increased and potentially permanent adverse health occurrences.

Impact of noise on laboratory findings

Since the human auditory system is an “open” system even during sleep, it receives a constant bombardment of noises.¹⁰ Humans are born with about 16,000 hair cells within the inner ear.³ Noises travel through the auditory system to the brain via the amygdala, which then affects the hypothalamic-pituitary-adrenal (HPA) axis, the regulator that releases stress hormones. Overstimulation results in increased levels of corticotropin

releasing hormone (CRH), adrenocorticotrophic hormone (ACTH), and cortisol.¹¹

Chronic activation of stress hormones can impact bodily functions and cause a number of health issues. Increased cortisol levels have been recorded in individuals living near airports with noise levels of 55-65 dB.¹¹ Increased cortisol levels can have a catabolic effect on protein from muscle, skin, and lymphoid tissues, while inhibiting transport and utilization of glucose.¹¹ Long-term noise exposure has also been associated with issues related to immunosuppression, insulin resistance, diabetes, cardiovascular disease, osteoporosis, and intestinal problems.^{1,6,11,12}

A study of noise exposure among production line workers over a period of five years showed that glucose and cholesterol levels were lower than a control group.¹³ Further, CBC results (WBC, RBC, HgB, HCT, MCV, MCH) tended to be higher than the control group. In other studies, noise exposure has been associated with imbalances of other blood components: magnesium, leukocytes (especially eosinophils and basophiles), blood viscosity, platelet count, lymphokines, triglycerides, sex hormones, and retention of sodium in the kidneys. These imbalances further exacerbate wound healing ability, abdominal obesity, pain medication management, stress dysmenorrhea, hyperandrogenicity in women, and reduced reproductive functions.^{6,11,14}

Impact of noise in healthcare settings

Florence Nightingale was quoted as saying, “Unnecessary noise is the cruel abuse of care which can be inflicted on the sick and the well.”^{14,15} Numerous studies have been done in the hospital setting looking at various noise sources and their impact on patients and staff. Emergency departments, ICUs, operating suites, and NICUs are just a few areas where noise levels can be elevated as part of daily routine activities.¹⁴⁻¹⁶

Noise disturbances that are common in laboratory settings include centrifuges, biosafety/chemical hoods, high-throughput instrumentation, vacuum pumps, and monitors. Other hospital areas are subjected to noise generating ventilators, suction machines, oscilloscopes, paging systems, and fire alarms. In addition, general conversation among staff, patients, and visitors adds to the din, as do TV sets, heavy doors opening and closing, computer printers, HVAC units, and noise associated with the moving of patients and equipment, medication carts, linen carts, and general housekeeping activities.^{14,17,18}

Anyone who has been a patient in a hospital knows that getting adequate sleep is often difficult. Average noise levels in a hospital may reach 60 dB or greater. Because patients sleep during the day as well as the night, monitoring noise levels throughout a 24-hour period may be required. The Global Health Organization, the WHO, and the Environmental Protection Agency (EPA) all recommend that noise levels within hospital units stay below 45 dB, and preferably no greater than 30 to 35 dB during the day and under 30 dB at night.^{14,17,18}

Studies have shown that excessive exposure to loud noises during pregnancy may result in high-frequency loss of hearing and potential slow growth development in newborns. It has been suggested that high noise levels can affect cochlear damage of infants in the NICU as well as



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proper growth development in premature infants. Women with occupational noise exposure of about 80dB were at risk for preterm delivery.^{1,18,19}

Noise control and prevention

Most laboratory equipment makers, building engineers, and employers are aware of the need to address occupational noise exposure through implementation of better engineering controls. In hospitals, noise levels can be attenuated to some degree with a careful review of systems and subsequent modification of noise-generating equipment with baffles, mufflers, and the like.²⁰ Hospital personnel should be actively aware of these and other noise sources and attempt to control noise levels by speaking in lowered voices, isolating noise-generating instruments, deactivating unnecessary monitor alarms, avoiding public paging systems, making better equipment selections, and initiating “quiet times.”

Knowing when one might be exposed to dangerous levels of noise requires testing by a professional and should be considered if the following circumstances occur within one's workplace:^{3,21}

- Do co-workers have to speak very loud to be heard?
- Do you have to turn the car radio volume higher on the way home as opposed to the drive to work?
- Do you have ringing in your ears after work hours?
- Do you have to ask your family/friends outside of work to repeat what they have just said?
- Do you have difficulty in hearing higher-pitched sounds, including the phone, doorbell, or alarm clock?

As individuals, we may have little direct control over most external noise sources. However, taking the time to recognize noise sources within our environment is the first step to reducing noise exposure within the laboratory, the hospital, and home. In some areas, local ordinances may provide oversight of noise control practices and should be explored if necessary. Noise Free America (www.noisefree.org), a nonprofit organization, focuses specifically on helping to resolve noise pollution issues.

Professional assistance in measuring noise levels may be sought when necessary. A quick way to determine the presence of chronic noise pollution is to use a sound meter app that is available for most smart phones.²² While the level of accuracy in measuring decibel levels may vary by phone type or the specific app used, it may serve as a basis for further action.

Be silent about noise no more!

While a number of regulatory agencies have issued guidelines addressing noise pollution on an industrial or metropolitan scale, it is incumbent upon all of us to recognize and minimize exposure to the various noise sources within our own environment—occupational and otherwise. The fact that studies show that excessive, chronic noise exposure has an effect on various lab analytes, which reflect significant health issues, only underscores the importance of this.

In 2011, the WHO issued a report²⁰ identifying the number of disability adjusted life-years (DALY, a measurement of the disease burden affecting longevity) lost due to excessive environmental noise in the European Union and the United States. These collective numbers should be a wake-up call to government agencies, employers, employees, and all healthcare workers to raise their level of awareness that noise pollution is a not-so-silent killer:

- 22,000 years for tinnitus
- 45,000 years for cognitive impairment in children
- 61,000 years for ischemic heart disease

- 654,000 years in general annoyance issues
- 903,000 years for sleep interferences
- One million years for traffic-related noise sources. 📢

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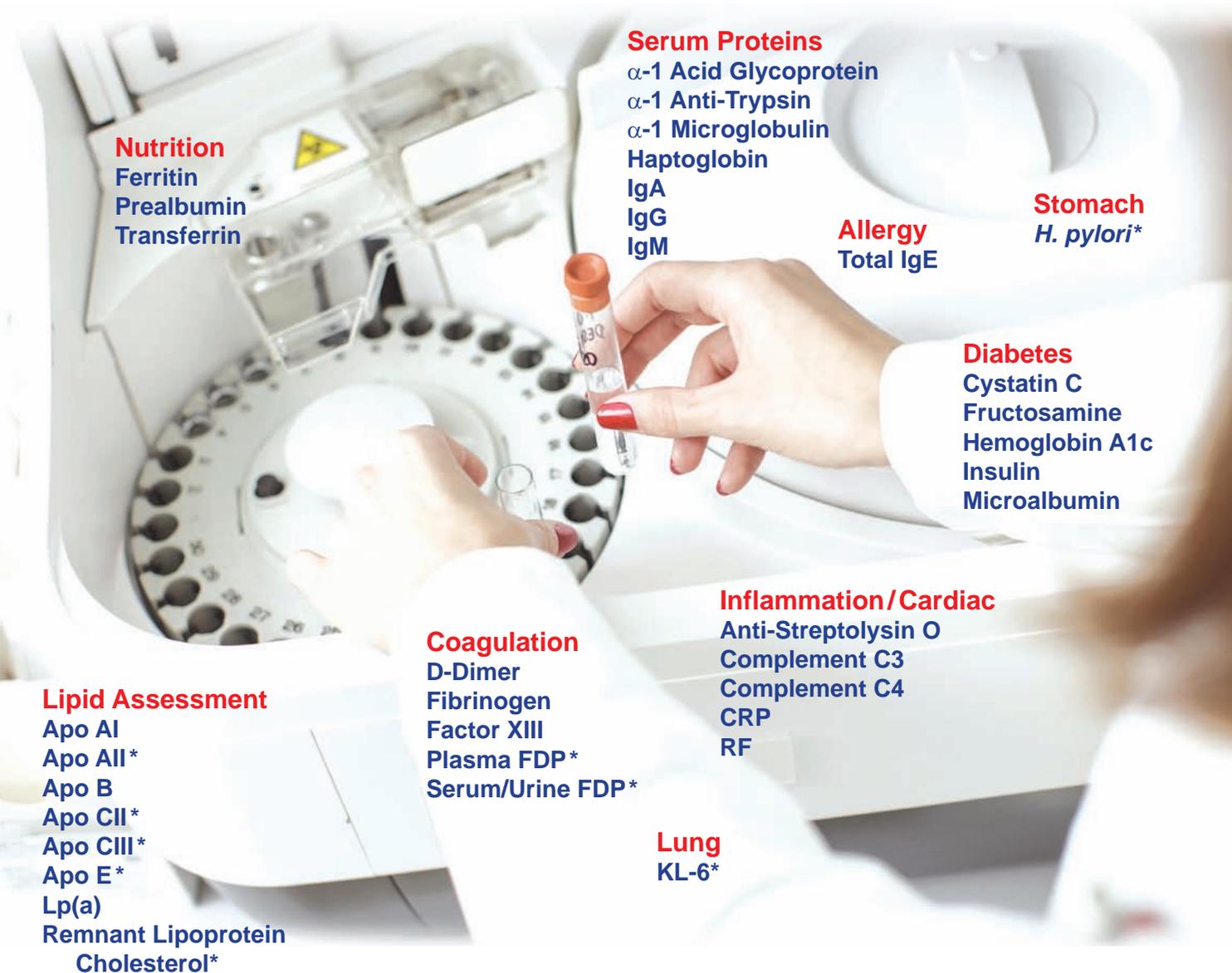


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What's the buzz in rapid testing?

A broad test menu and connectivity

There is an increasing need for clinicians to have access to the right test, in the right setting, at the right time. Above all, for rapid testing to have the most effective clinical impact on patient care, the results from point-of-care testing devices need to be accurate. This means that the test results are consistent with lab testing values to deliver concordant results that clinicians can trust. Reliability enables clinicians to rule out potential diagnoses more quickly. Rapid, informed diagnoses and treatment decisions at the patient-side ultimately aid in improving clinical outcomes.

A broad menu benefits clinical service lines that routinely perform blood analysis: for example, critical care units, emergency departments, radiology, and outpatient centers. The key advantage of a broad and simple test menu is that regardless of what tests are needed, the same analyzer and reagent will be used the same way, enabling a broad range of users to test with confidence. With a full menu that encompasses pH, partial pressure of oxygen, partial pressure of carbon dioxide, sodium, potassium, ionized calcium, hematocrit, glucose, lactate, creatinine, chloride, and BUN and TCO₂, clinicians can get a comprehensive view of patients' results quickly.

To remain relevant, rapid tests need to have connectivity capabilities so that the results and critical values can impact care in a timely manner. For this reason, a key trend with rapid testing is connectivity. An "always open" middle-ware philosophy will become increasingly pivotal to deliver critical results in a timely manner.

—Jason Weshler

Director of Marketing and Business for End-to-End Solutions
Point-of-Care Diagnostics, Siemens Healthineers

Breakthroughs needed in rapid POC testing

Rapid testing, particularly for point-of-care applications, has seen tremendous improvements in recent years. Still, there is a pressing need to do even better.

Consider critical care teams operating in remote locations, nursing homes, and other areas where hospital access is non-trivial. Today, "rapid testing" means emergency teams get patients to medical facilities, where physicians send samples to on-site clinical labs, which return results in a few hours. This process takes hours from the initial mayday to getting information that could shed light on patient treatment. What would make a real difference is tests that could be performed in the field, yielding results fast enough to adjust intervention and help determine whether a trip to the hospital is necessary.

Sepsis is a good example of how such a breakthrough would help. While most sepsis diagnostics take hours to identify the causal pathogen, there is an acute need for a rapid triage test that provides quantification of inflammation levels related to a sepsis diagnosis. This would tell first responders and Emergency Department staff whether to begin sepsis treatment protocols, a decision that must be made quickly to give the patient the best chance of survival. A portable, 15-minute sepsis test would do wonders for patient outcomes.

That's just one example to show that incremental improvements in rapid testing are not enough. Healthcare teams and lab professionals need new testing options that radically alter what's possible in order to deliver significantly improved patient care.

—David Ludvigson

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Legal liability in urine drug testing: Could your lab be exposed?

By Gerhard Pappert, PhD, Carlton Hoyt, PhD, and Yves-Vincent Duperron

The results of laboratory diagnostics have serious implications. A false positive or false negative of any kind can be potentially life-altering. False results in drugs-of-abuse testing can impact an individual's career advancement, lead to social stigmatization, and even mean the difference between freedom and imprisonment for the person involved.

In spite of rapid advances in laboratory science, drug tests are susceptible to manual and systemic errors. Even with the utmost care, it is not possible for analytical laboratories to achieve 100 percent correct results. Naturally, the question arises: to what extent can drug testing labs be liable for faulty results?

Labs' liability: an emerging legal consensus

Drug testing laboratories have, until recently, been largely unaccountable for erroneous test results. In recent years, however, labs have increasingly been taken to court and found liable for damages.

Many cases of drug testing laboratories successfully being sued are related to termination of employment. For instance, in *Landon v. Kroll Laboratory Specialists, Inc.*,¹ the plaintiff suffered termination of employment due to false-positive drug test results. He was given the right to sue on the grounds that the laboratory used a lower-than-recommended threshold for testing for the drug THC in the bloodstream. The court agreed that the lower standard warranted allowing Landon to sue Kroll Laboratories for "negligent testing."

In the *Sharpe v. St. Luke's Hospital* case,² an employee was fired due to a positive test result for cocaine from routine, random drug testing. The employee claimed that the chain of custody for her urine samples was adversely affected by numerous events which occurred at the hospital, as a result of which her specimen falsely tested positive. The case went through numerous judicial reviews. Eventually, the Pennsylvania Supreme Court ruled that the hospital "should have realized that any negligence with respect to the handling of the specimen could harm [the employee's] employment. The substantial harm deriving from inaccurate results (termination of gainful employment) would be a foreseeable consequence of a breach of the duty of reasonable care."

Laboratories have also been held liable for wrongful termination of employment due to false positive results in *Berry v. National Medical Services*³ and *Quisenberry v. Compass Vision*.⁴

Apart from workplace issues, drug testing providers are being sued for indirect harm to patients. In the case of *Devore v. Magee-Women's Hospital of the University of Pittsburgh Medical Center* the defendant settled with a mother who lost her newborn after an erroneous drug test.⁵ In a similar lawsuit, Jameson Hospital agreed to pay a \$143,500 settlement to a mother whose infant was

taken away from her family for five days based on a false positive drug test.⁵

There are many other foreseeable situations in which laboratories may be liable for damages due to incorrect test results. False positives are not the only danger in workplace drug testing. If workplace accidents occur due to an employee being under the influence of drugs, a false negative could similarly expose the laboratory to damages, as the person who caused the accident might not have been working if the diagnosis was correct. In therapeutic drug monitoring (TDM), misclassification of therapeutic compliance could lead to addiction or adverse events and similarly lead to liability exposure for laboratories. Those situations have not yet produced litigation, but they are, as the saying goes, "a lawsuit waiting to happen." This is a dangerous time for labs.

Strategies to mitigate risk

The first risk mitigation in any diagnostic setting comes from practicing simple safeguards such as ensuring correct patient identification and proper sample transport and storage. These safeguards, however, will not materially mitigate risks like the ones discussed above. Likewise, once the sample is injected for LC/MS analysis, it is too late to correct for many sources of error. Much of the risk mitigation must come down to the enzymatic hydrolysis.

Many drugs and substances subject to TDM are present in our bodies in a conjugated, glucuronidated form. Those include opiates, opioids, tricyclic antidepressants (TCAs), benzodiazepines, cannabinoids, and many new psychoactive substances. Therefore, β -glucuronidases are, by far, the most common enzymes used to cleave the analytes from the glucuronide and allow labs to effectively separate the drug compounds using liquid chromatography.

What many laboratories do not consider is just how varied these enzyme preparations are. Between the different species that β -glucuronidases are taken from, along with the recombinant and/or engineered variants which have been developed, there are dozens of commercially available β -glucuronidases from hundreds or potentially thousands that have been identified and purified. In any given β -glucuronidase preparation, the total protein content may differ by a factor of 10. The activity and specificity of β -glucuronidases may vary by a factor of five. The temperature and pH at which the enzyme is active often differ significantly. The buffers used may be different. These factors are critical in the outcome of the analysis.

Actionable and preventable sources of error

Many sources of analytical error have a basis in preventable preanalytical conditions and are due to unwanted reactions during sample preparation such as conversions, derivatizations, and binding, or are simply due to incomplete hydrolysis. Many can be predicted and rectified.

Heroin is commonly detected in urine as its unique metabolite 6-monoacetylmorphine (6-MAM) and its major metabolite morphine. Detection of 6-MAM has been considered the definitive evidence of heroin use.⁶ However, a false positive identification of heroin is possible when high levels of morphine are present in the urine samples and acetate buffer is used for enzymatic hydrolysis. When it is possible that morphine will be present, the use of enzyme preparations requiring acetate buffer should therefore be avoided.

A commonly overlooked source of preanalytical error in drug testing is the reductive transformation of benzodiazepines.^{7,8} The treatment of urinary oxazepam by β -glucuronidase enzyme preparations results in the production of nordiazepam (desmethyldiazepam) artifacts. This unusual reductive transformation also occurs in other benzodiazepines with a hydroxyl group at the C3 position, such as temazepam and lorazepam.⁷ Unlike acid-catalyzed hydrolysis, which is known to induce benzodiazepine degradation and transformation, the β -glucuronidase method was not known until recently to cause such transformations; however, it is not necessarily surprising considering that many β -glucuronidases are active at low pH conditions. Utilizing β -glucuronidases which are active at neutral pH is therefore important to ensure proper reporting of benzodiazepines. There is some evidence suggesting that TCAs are also labile under low pH conditions.

A number of compounds which are often critical to drug testing may become protein-bound in significant quantities. Fentanyl is especially prone to protein binding,⁹ but other opiates and opioids such as morphine¹⁰ and oxycodone¹⁰ also bind in significant quantities, having potential ramifications in TDM.

When analyzing any difficult-to-cleave analyte, such as opiates and opioids, the upper limit of quantitation (ULOQ) needs to be considered. Many protocols not only won't completely hydrolyze all glucuronidated analytes but fail to recognize this due to poor experimental planning, which leads to misplaced confidence in results. In order to ensure that the drugs are completely liberated from their glucuronide, careful selection of the hydrolysis control is necessary. The compound used as a hydrolysis control should be the hardest-to-recover compound within its class (for instance, codeine-6-glucuronide with opiates/opioids), and a compound from all classes should be utilized in case there is an effect which is unique to that class of compounds, such as acid lability. Only by using the conjugate from each class that is the most difficult to recover and seeing complete recovery of those controls can labs be confident that drugs of interest within the sample are also completely recovered. Using a highly active β -glucuronidase can help ensure complete hydrolysis as well as improve operational efficiency.

Being aware, being prepared

Test results from analytical laboratories are the basis for important decisions in medicine, forensics, workplace drug monitoring, and other areas. Consequently, results need to be correct and reproducible. The consequences of false-positive or false-negative results can be extreme for both laboratories and patients. Drug testing companies used to be largely unaccountable for their test results but now are increasingly held

liable and find themselves involved in lawsuits due to errors that are probably common throughout the industry and, in many cases, may be unknown to the laboratories analyzing the specimens. To minimize and mitigate these risks, laboratories must identify and eliminate sources of error with a special focus on preanalytical steps, where many errors originate. The preparation of urine specimens should be reevaluated in many laboratories, and consideration given to the enzymes and conditions used during hydrolysis. 

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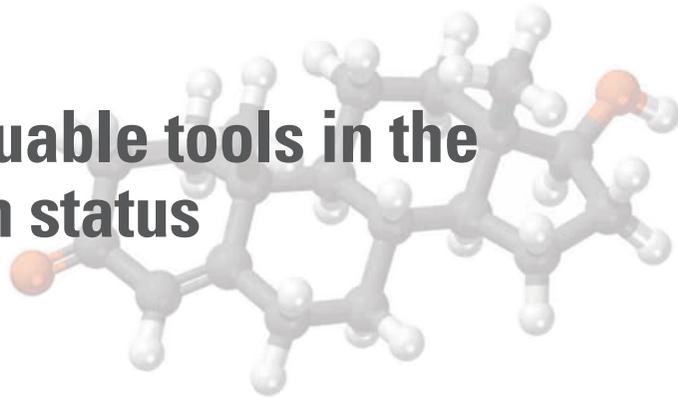
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SHBG and FAI are valuable tools in the diagnosis of androgen status

By Linda C. Rogers, PhD, DABCC, FACB



Testosterone is the principal male sex steroid hormone. It is produced mainly in the testes and is responsible for the development of male sex characteristics. In males, it is the hormone which develops secondary sex characteristics at puberty. Later in adulthood, testosterone affects sex drive, bone density, muscle size and strength, and red blood cell production. It also has an effect on mood, metabolism, and the cardiovascular system.

Testosterone is produced in smaller amounts by the ovaries in women. In both sexes, there is contribution from the adrenal cortex in the synthesis of other androgens which are precursors for testosterone. Assessment of androgen status is important in men for the diagnosis of hypogonadism and in women for the diagnosis of a variety of disorders including polycystic ovarian syndrome (PCOS). In both sexes, androgen status is important in the evaluation of adrenal disorders, particularly adrenal tumors and certain types of congenital adrenal hyperplasia.

Most clinical laboratories measure total testosterone by utilizing an immunoassay for the assessment of androgen status. Immunoassays are readily available with multiple manufacturers' reagents and instruments. When the total testosterone level assessment does not support a patient's clinical symptoms, the sample is usually referred to a laboratory that performs free testosterone by alternate methodology such as liquid chromatography/mass spectrometry (LC/MS), as most hospital laboratories have neither the instrumentation nor the technical expertise to perform mass spectrometry.

The referral process for the analysis of free testosterone is time-consuming and costly. An alternative to measuring free testosterone is the calculation of the free androgen index (FAI). This is a simple calculation of the ratio of total

testosterone and sex hormone binding globulin (SHBG) which provides an estimate of the bioavailable testosterone—that is, testosterone that is free (unbound to any protein) plus testosterone that is loosely bound to albumin.

Binding proteins and availability of hormone

SHBG is a high-affinity binding protein for androgens and estrogens. The majority of testosterone is bound to SHBG, which renders testosterone unavailable to tissue receptors. In normal adults about 55 percent of testosterone in men or estradiol in women is tightly bound to circulating SHBG and, therefore, unavailable to tissues. Most of the remaining hormone is loosely bound to bulk carrier proteins, primarily albumin, and is considered available to react with receptors. Only a small fraction of testosterone (about two percent in males, one to two percent in females) is “free” or unbound to any protein¹ and also available to tissues. Thus, both free and albumin-bound hormones are considered “bioavailable.” Unbound or free testosterone is the only form of the hormone that mediates its biological action at the target tissues in both sexes via receptors.

According to the “free hormone hypothesis,” SHBG modulates the bioactivity of sex steroids by limiting their diffusion into target tissues.² The free hormone hypothesis states that the biological activity of hormones is determined by their free (that is, non-protein-bound) concentrations. In the case of androgens and estrogens, free hormone concentrations and bioactivity are believed to be determined by SHBG. SHBG is a liver-secreted homodimeric glycoprotein with high affinity to both steroid hormones.

The FAI can be considered an estimate of the bioavailable hormone. With the availability of

immunoassays for both testosterone and SHBG, laboratories can perform these assays and provide an estimate of bioavailable testosterone via the calculation for FAI. This calculation for bioavailable testosterone may show a better correlation with clinical symptoms than total testosterone levels alone.

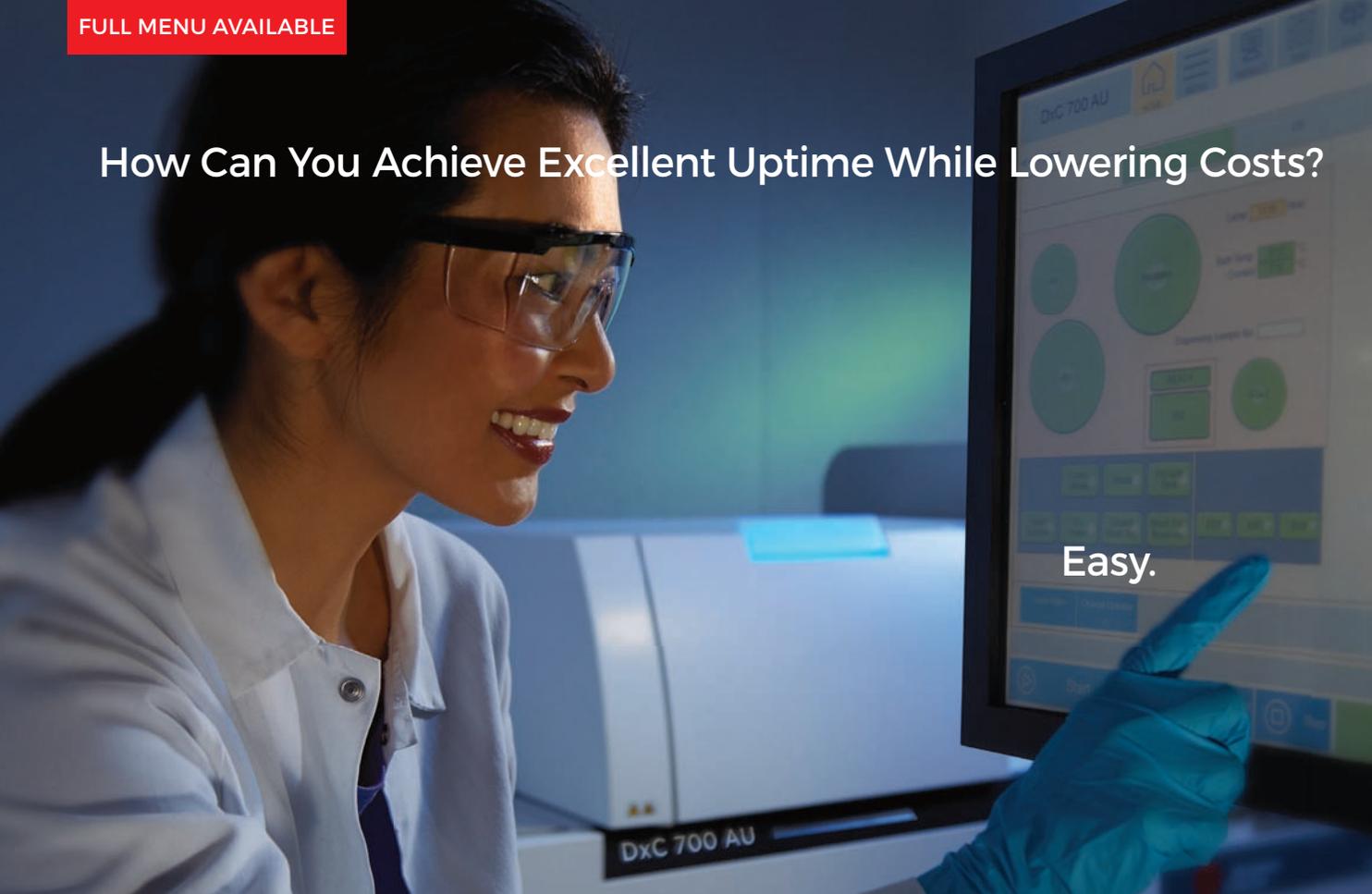
Utilization in men

The most common use of testosterone assays in males is to diagnose hypogonadism. Hypogonadism is defined as biochemically low testosterone levels along with clinical symptoms, which may include reduced sexual desire (libido) and activity, decreased spontaneous erections, decreased energy and depressed mood, reduced bone and muscle mass, and increased body fat. The term “andropause” is used to describe decreasing testosterone levels related to aging men. In general, older men tend to have lower testosterone levels than younger men. Although this is not universal, testosterone levels gradually decline throughout adulthood in males, on the average of about one to two percent a year.³ In addition to the decline in testosterone, an associated rise in SHBG levels has been documented.⁴ This rise in SHBG contributes to the decrease in bioavailable testosterone. A calculated FAI can aid in the assessment of andropause-related symptoms. In a retrospective study, Ring et al concluded that adding SHBG to total testosterone testing facilitated a more accurate diagnosis of male infertility associated with hypogonadism.⁵

According to the American Urological Association Position Statement on Testosterone Therapy, testosterone therapy is appropriate treatment for patients with clinically significant hypogonadism, including those with idiopathic clinical hypogonadism that may or may not be age-related.⁶ In recent years

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there has been an increased interest in testosterone therapy to reduce the symptoms associated with the decline in testosterone levels. For these patients, regular monitoring of testosterone is essential for management of dosage and symptom abatement. SHBG and FAI could add to the better management of andropause.

Utilization in women

Testosterone measurements in women are used for evaluating states of androgen excess to exclude androgen-producing tumors and to aid in the diagnosis of other hyperandrogenic states, the most important being PCOS, the most common endocrine disorder in females. The prevalence of PCOS varies depending on which criteria are used to make the diagnosis, but it is as high as 15 percent to 20 percent when the European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine criteria are used.⁷ PCOS is a common heterogeneous endocrine disorder characterized by irregular menses, hyperandrogenism, and polycystic

ovaries. According to guidelines published in 2013, the diagnosis of polycystic ovary syndrome is made if two of the three following criteria are met: androgen excess, ovulatory dysfunction, or polycystic ovaries.⁸ In peri-menopausal and postmenopausal women, the authors suggest that a presumptive diagnosis of PCOS can be based upon a well-documented long-term history of oligomenorrhea and hyperandrogenism during the reproductive years. The diagnosis of PCOS in an adolescent girl can be made based on the presence of clinical and/or biochemical evidence of hyperandrogenism (after exclusion of other pathologies) in the presence of persistent oligomenorrhea. Thus the measurement of testosterone is key to diagnosis.

An early study by Escobar-Morreale et al⁹ measured testosterone and SHBG and identified SHBG and FAI as the best assays for diagnosis with AUC 0.875 and 0.87 respectively. In a more recent study of 122 women with and without PCOS, measurements of total testosterone, SHBG, and calculated FAI were

compared. The authors concluded that FAI is a valuable laboratory assessment in the diagnosis of PCOS. In a study comparing tests and outcome, Miller et al found that the calculation of FAI correlates better than the more complex measurement of free testosterone in women for hypoandrogenism.¹⁰ Al Kindi and colleagues concluded that FAI is superior for the diagnosis of hyperandrogenism in women to total testosterone alone.¹¹ Thus FAI can be an important tool in assessing the androgenic state in the female population and, in particular, women with PCOS.

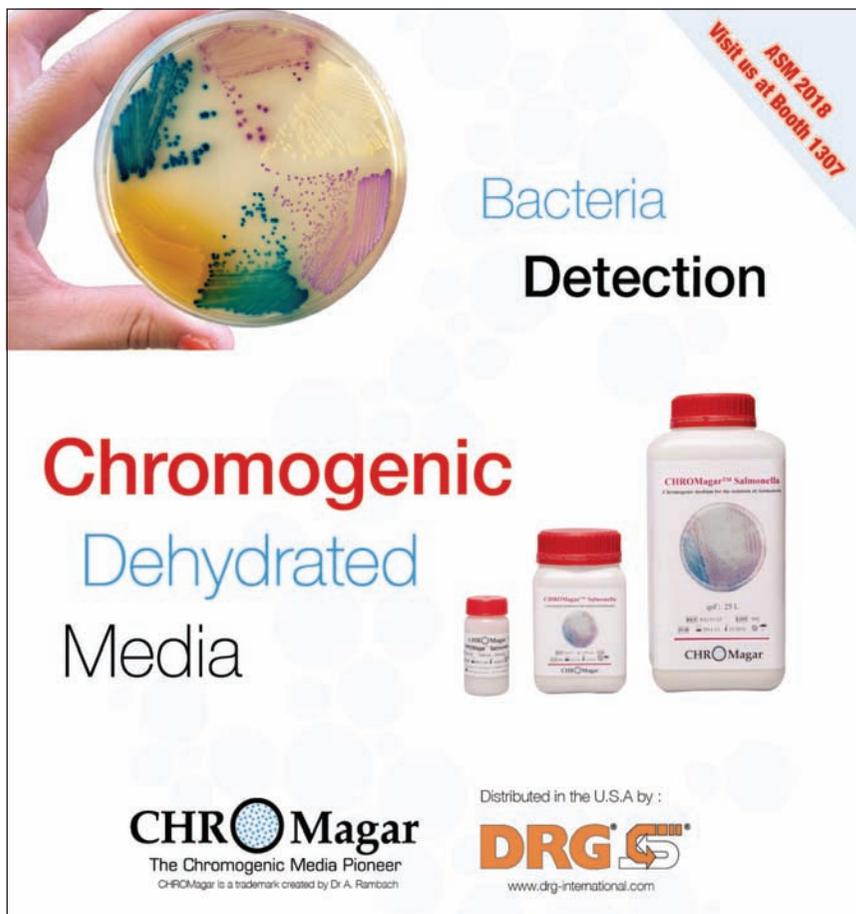
Utilization in children

In boys, testosterone measurements are used during adolescence in the evaluation of early or delayed puberty or at birth during the evaluation of under-virilized males. In girls, testosterone assays are used to assess and treat disorders of sexual development and in the evaluation of contra-sexual pubertal development. As in women, testosterone determination in children should be carried out only with assays of sufficient sensitivity and in conjunction with appropriate normative data. The measurement of SHBG and calculating FAI may be underutilized in the assessment of androgen status in children.

Utilization of SHBG alone

Until recently, the sole function of SHBG was thought to be transport of sex steroids. As discussed previously, the measurement of SHBG can be used to estimate bioavailable testosterone levels in patients suffering from either too little or excessive androgen exposure.

New information suggests that SHBG may have broader utility in assessing the risk for endocrine diseases and the clinical consequences of the metabolic syndrome, namely, type 2 diabetes and cardiovascular disease. An association between SHBG and insulin resistance is reported across many longitudinal and cross-sectional studies. A recent review discusses the evidence.¹² In a recent nested case control study of postmenopausal women from a cohort of the Women's Health Study and a cohort of men from the Physicians' Health Study II of men, Ding et al concluded that low circulating levels of SHBG are a strong



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predictor of the risk of type 2 diabetes in both women and men.¹³ They suggested that SHBG could be an important target in stratification for the risk of type 2 diabetes and for early intervention.

SHBG has also been associated with the development of gestational diabetes (GD). GD is a common pregnancy complication that is associated with increased maternal and neonatal morbidity. Identifying and treating these women is important to improve outcomes. In a recent case-controlled study, researchers found that patients with GD have lower circulating levels of SHBG than normally glucose-tolerant pregnant women and concluded that circulating concentrations of SHBG represent a potentially useful new biomarker for prediction of risk of GD beyond the currently established clinical and demographic risk factors.¹⁴ The authors also established a cut-off value for SHBG which had 90 percent sensitivity and nine percent specificity for diagnosis. Whether SHBG can be used to replace the diagnosis of gestational diabetes is yet to be determined.

Several recent studies have shown a relationship between SHBG and metabolic syndrome. Metabolic syndrome consists of a set of factors that confer increased risk of cardiovascular diseases, including obesity (especially abdominal obesity), insulin resistance, dyslipidemia (increased triglyceride levels and reduced HDL cholesterol levels), and systemic arterial hypertension. In an early study of older men, Chubb and colleagues concluded that low SHBG is more strongly associated with metabolic syndrome than low total testosterone.¹⁵ In a subsequent retrospective study, Callou de Sa and colleagues also concluded that low serum levels of SHBG are associated with a higher prevalence of metabolic syndrome among male patients.¹

A review of SHBG in children and adolescents has been provided by Ayden and Winters.¹⁷ Although more research is needed in children, the authors determined, "Evidence is accumulating that low SHBG levels are an indicator of insulin resistance, and SHBG may be an easy-to-measure and clinically useful biomarker for the early identification of children who are

destined to develop obesity-related chronic diseases."

FAI and SHBG

The calculation of FAI can be an important addition to the laboratory diagnosis of androgen status and may be more beneficial than measuring total testosterone alone. In addition to its use in the calculation of FAI, there is increasing evidence in the literature to suggest that SHBG levels are correlated with multiple

medical conditions. It remains to be determined whether SHBG is solely a biomarker, or if it actively participates in the pathogenesis of metabolic disease. 

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Field-portable MDx

By John Brunstein, PhD

There is an enduring appeal to the concept of point-of-care (POC) or near-POC diagnostic methods. Having the ability to perform a diagnostic test in the doctor's office while a patient is present, rather than having to send a sample off to a centralized lab for testing, means that what would otherwise need to be two patient visits could be replaced by a single session. It also suggests the potential for a more timely response with a specific rather than empirical treatment strategy, with particular implications for the appropriate, limited use of antibiotics. Carrying the POC concept a step further, one can imagine the potential utility if cheap, effective, reliable diagnostic systems could be made small, portable, simple, and rugged enough for use in low-resource settings, where they might have the greatest human impact.

Of course, many such diagnostic methods exist, but they are most frequently some form of a rapid immunological test. While these excel in simplicity, low cost, and speed, they generally lack the sensitivity and specificity that a molecular method would provide. That they are so widely used even with these shortcomings underscores the need for POC/near-POC testing and the potential for growth in this field if suitable molecular devices and tests can be developed. (If you wanted to put numbers on this potential, a 2016 report by Grand View Research predicts a global market of \$3.9B in POC molecular by 2024.¹)

Challenges to POC MDx

The challenges that face POC or more ruggedized field portable MDx use are significant. Extreme sensitivity also means extreme sensitivity to contamination; reagents may have limited shelf life without refrigeration; some form of sample extraction/release of nucleic acids is required as an initial step; and interpretation of results may require in-depth expertise and familiarity with the assay.

Increasingly, however, there are approaches that address those challenges. Foremost among these is the designing of systems around unitary disposable cartridges that combine sample extraction with molecular processing and detection. Use of stabilized (likely, lyophilized) reagents inside such a cartridge addresses the stability issue. Interpretational complexity can be simplified through the use of multiplexing (in-reaction controls for sample inhibition, reagent function, sample sufficiency, and extraction function). As we take an overview of currently available and some in-development POC/portable molecular MDx platforms, it should not come as a surprise to see that these design features are present.

What's out there now

What, then, are some of the currently available FDA-approved systems that could pass for field portable MDx?

The Cepheid GeneXpert Omni is based around the same unitary cartridges used in the other GeneXpert systems,

which were the first approved "sample-to-answer" device on the market. While one might be tempted to consider this technology to be a bit long in the tooth, the manufacturer's claim of it being "proven technology" is indisputable. These particular assays have been around long enough to be well understood and are available for a wide range of targets, including many of interest in low-resource settings. In contrast to the other, lab-environment versions of the GeneXpert platform (which range from moderate benchtop to wall filling, depending on throughput), the Omni is intended as a field portable stand-alone unit. It weighs barely two pounds and is small enough to fit in an airplane carry-on with a supply of cartridges, a pipettor and some tips, and a box of gloves. It includes integral battery power (claimed operational life, four hours) which can be supplemented with additional larger capacity rechargeable battery packs, allowing for extended day or even multi-day use in remote settings. The device handles its own data storage needs, making for an appealing package if there's a cartridge for your test of interest and you want to bring reliable rapid molecular testing to low-resource settings.

Another system that the reader may have come across, as it's been around for several years, is Roche's cobas Liat ("Lab in a Tube") System. Accurately described by its manufacturer as being "about the size of a single-serve coffee maker," and complete with a small display screen showing results of the core real-time PCR technology, this system has tests available for a number of applications in infectious diseases and has sample-to-answer turnaround times on the order of 15 to 30 minutes. While this device does require external power, the consumption is low; a small battery pack with integrated inverter could provide required portable off-grid power. A larger challenge to remote application of this device—with current assays—is the need for refrigeration, but for a day out in the field away from infrastructure, a cooler and cold packs or ice would suffice. And even with these add-ons, the whole package is vehicle-portable for use for hours to possibly a few days in low-resource settings.

Another example, not really designed for "in the field" use but more targeted to the physician office (it's described as "near-patient testing") MDx setting, is the Alere I system. If the definition of "field-portable" were expanded to include, say, labs shoehorned into a portable lab along the lines of a converted recreational vehicle, this system could be included in our list, with at present two CLIA waived assays available.

Also by that expanded definition, another system that has been around for a while and would fit the bill is the Biofire (bioMérieux) FilmArray. With a softwall pouch cartridge format allowing for rollers to enact in-pouch fluidics by moving solutions between various pouch subchambers, allowing for extraction, amplification, and finally microarray hybridization and detection, this system may be the most

multiplex-capable of the systems we are considering. Its cleared available assays make use of that in the form of multitarget symptomatic-based panels for respiratory, GI, positive blood culture, and meningitis/encephalitis presentations.

What may be coming

A theme that is common to these devices is integration of small, low-power computer, optical, and mechanical/thermal control systems. As device engineering advances make these subsystems smaller, less expensive, more power-efficient, and more reliable, we should expect to see more portable MDx devices emerge to take advantage of this. A number of as-yet uncleared/unapproved devices are publicly in development. That is a process that can notoriously take longer than hoped for or expected by the developer(s), so expect them when you see them.

A necessarily incomplete list of some of these would include the QuantuMDx Q-POC (intended to be freestanding, cassette-based, and battery-operated and provide sample-to-answer multiplex MDx capabilities); the LaCAR LC-Genie (battery-powered, based around 8-well strip tubes, and intended for SNP assays on already extracted nucleic acid samples); the DxNA GeneSTAT cartridge-based real-time PCR system, which is not battery-powered but can operate in a laptop-free, self-contained mode and which employs RFID tagged cartridges with lyophilized reagents for stability and minimal user training requirements; the ERBA Molecular Lumora PDQ, based on isothermal amplification with luminescent monitoring of real-time target amplification for up to 96 samples at a time; and the Ahram Biosystems' Palm PCR S1, a 24-well, 6-optical channel real-time PCR machine with integrated display that includes an internal battery capable of supporting ~4 hours operation (or 200 tests, according to the manufacturer).

Doubtless there are many other similar designs on drawing boards and in various stages of prototyping around the world, and while not all of these may make it to market, as end users we should be encouraged that so much interest and effort is being employed in bringing simplified, portable MDx to clinical needs. An analogy to the delivery of telephone services in the third world is apt; in that case, the explosion of cheap cellular technology meant that in many remote places the first available telephone systems have not been old-fashioned wired networks; rather, these locations went from nothing directly to cellular systems. Similarly we may find that low-resource settings may pass right over antigen-based systems and, through portable MDx, go directly to high-sensitivity and high-specificity molecular methods in the near future. In settings that are less remote but still dependent on central labs, we should expect to see a similar emergence of at least a limited number of simple but high-value POC molecular tests that will both speed up time to appropriate care and reduce "simple" workload for core labs. Such core labs should see this as an opportunity that frees them up to focus resources on the development and performance of emerging tests that still require extensive instrumentation, staff training, bioinformatics, and other infrastructure—such as many next generation sequencing (NGS) applications.

The expected emergence of such portable/POC MDx devices to take on aspects of a core lab will not be without some shortcomings. One which regular readers of this column may recall being raised before is that sample-to-answer instruments—or at least, all the ones this author has familiarity with—don't

allow for subsequent alternative use of any nucleic acid extract prepared on-system. (There's a good reason for this; the entire function of sealed, single-use cartridge format assays in avoiding PCR contamination would be compromised if they could be opened and closed at will). This can be a disadvantage for scenarios where limited sample is available, such as pediatric CSF, and a negative test result is obtained. Unlike a full core lab with separated nucleic acid extraction and testing capacities that allow for subsequent extract redirection to additional or confirmatory testing, these portable/POC/all-in-one devices require a whole new sample (or at least aliquot thereof) to perform another test.

Regardless of such shortcomings, though, the benefits inherent in moving the accuracy and power of MDx closer to the patient, in small hospitals or rural settings, will continue to drive the development of portable simple use technology for a range of clinical applications. We should expect to see such systems become increasingly common. 🔄

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John Brunstein, PhD, is a member of the MLO, Editorial Advisory Board. He serves as President and Chief Science Officer for British Columbia-based **PathoID, Inc.**, which provides consulting for development and validation of molecular assays.

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A perspective about the rarity of biotin interference and mitigating risk

Diagnostics are foundational to medical decision-making, so we appreciate healthy scientific and clinical dialogue about reducing lab errors, including interferences such as biotin. The article by Dr. Ramani Wonderling, “A closer look at the recent FDA safety communication about biotin interference” (*MLO*. 2018;50(3):44-45), however, missed the opportunity to provide up-to-date data about biotin use and its pharmacokinetics or practical direction.

It is first important to provide real-world perspective on biotin use today, as data from 2017 reporting biotin sales may be reassuring to laboratorians and clinicians. Over a three-year period (July 2014-June 2017), biotin sales in the United States have been trending slightly upward, with the steadiest growth in doses 2.5 mg and under, levels that pose a very low risk to lead to interference. Sales of 5 mg doses have declined, according to Nielsen FDM Data ending June 2017.¹

In terms of evaluating the extent of biotin use, it's also valuable to note that in May 2017, a manufacturer of high-dose biotin (corresponding to 10,000 times the recommended daily intake of biotin) withdrew its application for the treatment of progressive multiple sclerosis.² Therefore, while over-the-counter biotin can be recommended as a treatment due to its benefits in metabolism-related disorders, there is no available, approved prescription high-dose biotin for the treatment of any disorder.

Second, a pharmacokinetic study, also published in 2017³ (doi.org/10.4155/ipk-2017-0013), provides clarity and useful guidance to laboratories regarding biotin doses and washout periods.

Topline findings are:

- Biotin as one ingredient within a daily multivitamin (30–40 mcg) has no effect on assays.
- 100 percent of subjects in the study taking 5 mg of biotin per day are below a tolerance threshold of 30 ng/mL within 3.5 hours.
- 100 percent of subjects in the study taking 10 mg of biotin per day are below a tolerance threshold of 30 ng/mL within eight hours.
- Subjects taking 20 mg of biotin per day may need to discontinue biotin intake for longer than eight hours prior to testing.

Also supported by a rich body of robust, clinical evidence is the reason most manufacturers utilize the biotin-streptavidin design for their assays: it offers the strongest, non-covalent biological interaction known. The strength and specificity of this interaction has led it to be one of the most widely used affinity pairs in molecular, immunological and cellular assays.

To date, we know of no confirmed cases of biotin interference violating our company's label claims. For perspective, globally, of the more than 1.4 billion thyroid tests, and 4.1 billion electrochemiluminescence assays performed between 2016 and 2017, we are aware of 32 cases where



biotin concentrations above the threshold stated in the package insert affected the results of the test. This is an extremely low incidence of confirmed interference.⁴

The potential for interferences affects all laboratory tests and has always been part of the narrative. All major manufacturers have assay menus where biotin might influence test results. No assay is “invulnerable,” as suggested by Dr. Wonderling.

There are many established ways to mitigate interference potential, such as following direction provided in the package inserts and serial testing in acute situations, e.g., patients with suspected myocardial infarction, per American Heart Association and American College of Cardiology guidelines as well as institution departmental policies. Increased awareness and education, as recommended in the November 2017 FDA Safety Communication,⁵ can only result in reduced errors and more informed clinical decision-making.

We support a full range of educational efforts and best-practice exchange for how laboratorians can mitigate risks as well as educate physicians and patients about reporting biotin use. 🔄

— Christopher A. Bird, PhD
Head of Medical and Scientific Affairs
Roche Diagnostics Corporation

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¹ CDC Weekly U.S. Influenza Surveillance Report. Available at: <https://www.cdc.gov/flu/weekly/>. Accessed on March 12, 2018.
² Rapid diagnostic testing for influenza: Information for health care professionals. Centers for Disease Control and Prevention website. <http://www.cdc.gov/flu/professionals/diagnosis/rapidclin.htm#table> Accessed March 12, 2018.
³ Roche **cobas**[®] Liat[®] Influenza A/B Package Insert



Cost management tips to offset reimbursement cuts

By MLO staff

The Centers for Medicare and Medicaid Services (CMS) released its final rates for the Clinical Laboratory Fee Schedule (CLFS) that phased-in a significant cut in the rates of those common tests physicians use every day to diagnose and treat patients.

The first cut, up to 10 percent, was effective January 1, 2018, with additional possible 10 percent cuts to come each year through 2020, and up to 15 percent each year for 3 years after that. The CLFS is based on information reported under the 2014 Protecting Access to Medicare Act (PAMA). PAMA revised the Medicare reimbursement methodology for clinical diagnostic laboratory tests. According to one industry estimate, the significant impact on laboratory margins is only now becoming clear. According to one estimate, a 10 percent cut in the CLFS will result in a 3-4 percent drop in laboratory profit margins.

Two laboratory-focused group purchasing organization executives weighed in on cost management to offset reimbursement cuts.¹



Labs need to verify they are efficient

Donna Showers, Senior Director, Lab/DI Specialists, Intalere, offered these tips:

- Provide contract review, product standardization for one or multiple laboratories (within an IDN or laboratory alliance) and/or distributor optimization and consolidation. Depending on their level of sophistication, labs can save significant costs by aggregating spend through a regional laboratory alliance group or understanding and using their distributor relationships properly. Your distribution partner should be able to help you understand the cost and efficiency advantage of utilizing their distribution model as the best source of procuring product whether it is through pricing advantage, elimination of added transportation charges, improving overall tier slotting on the distribution contract, and reduction in the number of purchase orders generated and managed.

- Examine overall laboratory profitability of both in-house and outsourced testing. This includes an in-depth make-versus-buy assessment to help your lab understand both the costs of performing tests (to include both supply and labor costs) as well as the profitability of those tests by determining payer mix and payer rates. The same assessment should be performed on those tests that are outsourced to a commercial reference lab. Based on staffing levels, equipment available, and most importantly, how testing and turnaround times affect patient care, the lab can determine which tests should be done in-house versus outsourced. For example, in one of the labs we examined, we determined that the lab could generate an additional \$200,000 in revenues as a result of the findings of our make-versus-buy assessment. One final process to the make-versus-buy assessment would be to conduct an RFP for the remaining reference lab testing; try to consolidate the number of reference labs that are used for the purposes of streamlining send out operations as well as realizing better pricing through economies of scale.

- It's not all about product necessarily. Workflow and laboratory design evaluation can make huge differences in improved efficiency and productivity.

- Many lab professionals are challenged with a lack of

ability to verify pricing accuracy on their purchases. Using software to identify and resolve pricing variances as quickly as possible can help reduce costs, eliminate future errors and improve overall price accuracy.

- Introduce Revenue Cycle Management. Laboratory managers should be corresponding with their billing departments. Laboratory outreach is often an overlooked revenue center in hospitals. Hospital information systems may not have the capability of measuring lab fiscal performance. The lab needs to have more control over their RCM process due to the payer-related nuances that are unique to lab. With appropriate software, coding expertise, collection strategies and denials management, the lab has the ability to improve their revenues by up to 20 percent to 30 percent.



Look for help from your supply chain experts

Akiva Faerber, Senior Principal, Vizient Inc., offered his suggestions for collaboration:

- Partner with the supply chain team and consistently introduce competitive new supplies, services options/levels that are less expensive

but meet the needs of the lab or that have the potential to improve performance.

- Work with manufacturers to enable the lab to conduct side-by-side evaluations of testing equipment to determine best platform. These side-by-side evaluations provide valuable insight in terms of floor space, technical ease of operation, test capabilities in terms of test mix and volume capacity, reliability, ease of customer capable maintenance and logistics. This also gives the lab staff the ability to have a "hands-on" assessment of the quality of the service staff in the event of platform failures.

- Negotiate and facilitate onsite training and train-the-trainer learning opportunities. Include these as part of the contract to eliminate add-on expenses should initial training found to be not adequate.

- Facilitate the frequency and ease of QA/QC, sequestration of reagents, information system interfacing.

- Entertain, educate and encourage vendors/providers to bring new lab-related products and services to lab for evaluation.

- Explore the option for support subject matter experts in lab to assist with efficiency, reducing costs, increasing revenue, performing coding billing and compliance opportunities, validation of LIS, Lean projects and improve TAT root cause analysis beyond lab. Ideally, there would be one SME from the vendor to assist with those tasks and one or two consultants to provide operational support.

- Assist lab department leadership in leveraging the benefits of point-of-care testing and cost versus traditional laboratory platform testing.

- Provide just-in-time agency staffing and interim management as necessary. Provide assessments as request for options related to outsourcing of laboratory management or sale of lab to commercial provider as well as review and negotiate pathology LLC contracts.

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GloCyte, www.rsleads.com/806ml-150

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Automated immunoassay instrument



Fujirebio presents the LUMIPULSE G1200, a mid-sized, fully automated immunoassay instrument. The LUMIPULSE G1200 is based on CLEIA (chemiluminescent enzyme immunoassay) technology. The system is capable of continuous loading and unloading of samples, reagents, and consumables without operational interruption. It utilizes individual test cartridges to reduce reagent waste and eliminate cross contamination, with a throughput of 120 tests per hour. Its assay menu is composed of a variety of areas including oncology, metabolic, neurodegenerative disease, infectious disease, thyroid, fertility, diabetes, and bone metabolism.

Fujirebio, www.rsleads.com/806ml-152

Hematology analyzer



The BC-5390 is a five-part differential hematology analyzer with built-in autoloader and a single closed tube sample mode. The hemoglobin analysis is performed using cyanide-free reagent. The analyzer processes up to 60 samples per hour and stores up to

100,000 results with histograms and Scattergram. The barcode reader and optional LIS connectivity enable seamless sample data transmission. Nearly all scheduled maintenance procedures are automated by touch buttons. The intuitive software enhances workflow efficiency and provides operators with a pleasant user experience.

Mindray, www.rsleads.com/806ml-153

Critical care blood gas analyzer



Nova's Stat Profile Prime Plus* is a comprehensive, whole blood critical care analyzer that offers blood gases, electrolytes, metabolites, co-oximetry, and 32 calculated results in a simple, compact device. Prime Plus combines maintenance-free, replaceable cartridge technology for sensors and reagents with patented, maintenance-free, and non-lysing whole blood co-oximetry technology. Test menu includes pH, PCO₂, PO₂, Na, K, Cl, iCa, iMg, Glu, Lac, Urea, Creatinine, Hct, Hb, SO₂%, and Co-Ox. *FDA clearance pending

Nova Biomedical, www.rsleads.com/806ml-154

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Medical Electronic Systems, www.rsleads.com/806ml-155

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Siemens, www.rsleads.com/806ml-156

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American Board of Bioanalysis provides certification for clinical and public health lab directors

What is the mission of the American Board of Bioanalysis? How does ABB serve the clinical lab community? The mission of ABB is to identify individuals who are qualified to direct and supervise clinical, public health, and bioanalytical laboratories.

ABB serves the clinical laboratory community by establishing education, experience, training, examination, and other qualifications that individuals must meet to qualify for ABB's director and supervisor certifications; determining and identifying which individuals meet those criteria; and providing a means for patients, physicians, employers, government agencies, accrediting agencies, and other interested parties to verify which individuals are certified by ABB.

How does ABB certify laboratorians who wish to advance in the clinical laboratory profession? What is the typical process? ABB certifies individuals by reviewing and verifying an individ-



Brooks A. Keel, PhD, HCLD(ABB)
Chairman of the Board
American Board of Bioanalysis

Professional

Dr. Keel is President of Augusta University (AU) and CEO of AU Health System. Previously, he has held administrative positions at Georgia Southern University, LSU, FSU, and the Kansas University School Of Medicine-Wichita, where he was also director of Reproductive Medicine Laboratories. Dr. Keel has more than 20 years of clinical laboratory experience, and has been certified by the ABB as a High-complexity Clinical Laboratory Director (HCLD) since 1987.

Education

BS, Augusta College; PhD, Medical College of Georgia; Postdoctoral Studies at UT Houston Medical Center, and University of South Dakota School of Medicine.

Personal

Nationally, Dr. Keel chairs the Board of Directors of the ABB, and serves on the Scientific Advisory Board of the AAB Proficiency Testing Service. He has authored 65 peer reviewed scientific publications, 78 peer reviewed abstracts, 19 book chapters and edited four books in the area of reproductive medicine and biology, and has served as PI or Co-PI on externally funded grants and contracts totaling over \$26 million. Dr. Keel is married to Tammie Schalue, PhD, an accomplished scientist and scholar.

ual's educational coursework; analyzing and verifying an individual's work experience, training, and continuing education; and preparing, administering, and maintaining an examination program to determine an individual's knowledge of relevant clinical laboratory technical disciplines, and, for directors, their knowledge of laboratory administration and management.

The process requires submission and review of an application by the ABB Board of Directors; receiving educational transcripts and employment verifications directly from the source; passing relevant examinations; and once certified, documenting continuing education units (CEUs) to maintain certification.

When was ABB established? What needs was the organization created to address? ABB was established in 1968 to provide a nationally recognized certifying board for generalist and specialist clinical laboratory directors/supervisors under the federal Medicare/CLIA and state statutes and regulations, and the requirements of private accrediting organizations.

How has ABB responded over the years to changes in federal regulations and other national and state oversight? Have new certifications been added?

ABB modified its certification categories to be consistent with changes in the CLIA '67 and CLIA '88 regulations, for example, by changing the director certification designation from CLD (Clinical Laboratory Director) to HCLD (High-complexity Clinical Laboratory Director).

Certification in several new technical disciplines has been added—for example, andrology, embryology, molecular diagnostics, and public health microbiology.

How is ABB addressing the aging laboratory workforce, and how is it affecting your work? ABB has championed, and continues to champion, a flexible career ladder that provides a variety of pathways for young laboratorians to enter into and advance within the clinical laboratory workforce.

What are some other broad industry trends and contexts that ABB is addressing? ABB has added technical disciplines that reflect important technological advancements in the laboratory industry, such as molecular diagnostics. The organization has also incorporated these new technologies

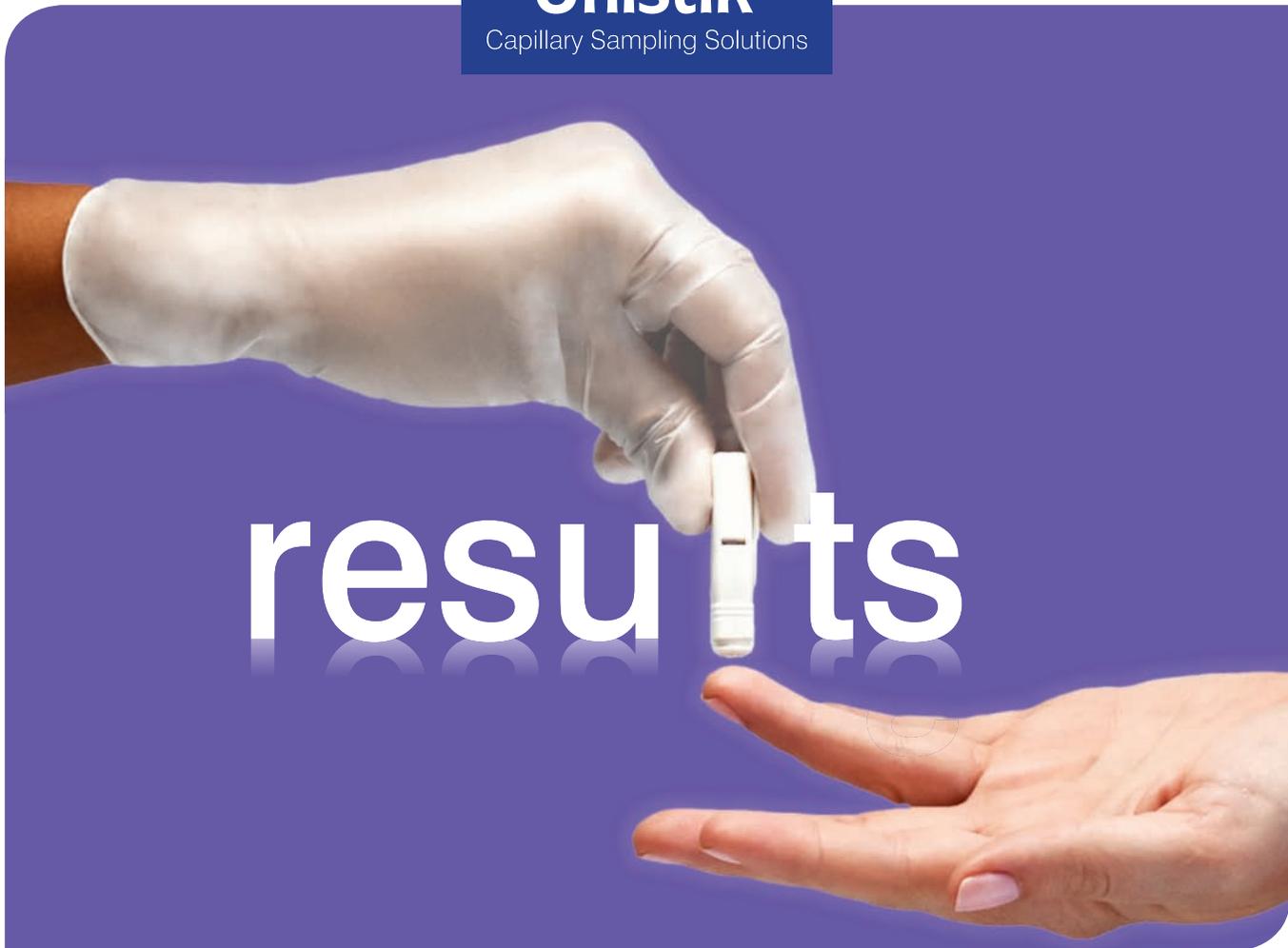
into its certification qualifications and examinations.

You have had a distinguished career as a scientist, educator, and now president of Augusta University. How has your work in academia informed your work with ABB? During my career, I have worn the Lab Coat of a Clinical Bench Tech, the "Tweed Coat" of a College Professor, and the Suit Coat of a University Administrator. This has given me unique insight into the various aspects of clinical laboratory training, practice, and regulation.

I began my career in assisted reproductive laboratory technology (ART) clinical laboratories in the mid-1980s, having had quite a few years of previous experience in a general hospital clinical laboratory setting. At that time, virtually all ART clinical labs were directed and staffed by individuals who had a great deal of reproductive biology knowledge but often had little to no experience in general clinical laboratory medicine. This often made the certification process for these ART-specific individuals difficult.

I approached ABB to determine if they would consider offering certifications to individuals in specific areas (like andrology and embryology) and judging the applicant's specific ART experience instead of requiring broad clinical laboratory knowledge in areas such as hematology, chemistry, and microbiology. The ABB Board agreed with this concept, and in the early 1990s adopted new certification standards recognizing categories of directors and supervisors that encompassed the specific disciplines of ART as well as the more classical areas of general lab medicine. This new certification process included the development of comprehensive general clinical lab knowledge and discipline-specific examinations.

Working with the ABB and the American Association of Bioanalysts, we have since sponsored comprehensive review courses and annual scientific and educational conferences aimed at providing continuing education opportunities for ART laboratory professionals, preparing candidates for ABB Certification Examinations, and enhancing the overall practice of clinical laboratory ART. Thus, my experience as an academician and an administrator, coupled with my years of experience at the clinical laboratory bench, has helped shape the certification processes now employed by the ABB, resulting in the certification of hundreds of clinical laboratorians throughout the U.S. and, indeed, across the world. 🔄



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